Comparison of clinical non-commercial tools for automated quantification of myocardial blood flow using oxygen-15-labelled water PET/CT

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Aims
Absolute quantification of myocardial blood flow (MBF) with $^{15}$O-water cardiac positron emission tomography (PET)/CT has recently demonstrated to hold promising diagnostic value for the detection of coronary artery disease (CAD). However, methodological differences in utilized analysis software packages (SP) could affect generated MBF values, potentially prohibiting widespread clinical applicability of obtained normal thresholds. The aim of this study was to compare two validated non-commercial SP, Carimas and Cardiac VUer, for the quantification of MBF using $^{15}$O-water PET.

Methods and results
One hundred patients with intermediate likelihood of CAD and scanned in academic centres in Amsterdam (n = 50) and Turku (n = 50) were included in the study. Patients underwent a $^{15}$O-water PET/CT scan during rest and vasodilator stress based on clinical indications. A single observer, blinded from clinical results and with no prior experience in either SP, analysed all patients twice with both SP. Reproducibility of each SP was assessed using intraclass correlation coefficients (ICC). Intersoftware agreement was assessed using paired t-tests and linear regression. ICC was excellent for each SP for both global and regional MBF (ICC > 0.90). Global MBF was comparable between Carimas and Cardiac VUer during rest (1.02 ± 0.28 vs. 0.99 ± 0.23 mL min$^{-1}$ g$^{-1}$, respectively, P = 0.07), and slightly higher for Carimas during stress (2.73 ± 0.82 vs. 2.63 ± 0.84 mL min$^{-1}$ g$^{-1}$, respectively, P = 0.01). At a regional level, for resting conditions small (<10%) but significant discrepancies were noted in each vascular territory while for stress MBF, a significant difference was only observed for the LAD region. Differences between SP for the LAD territory were abolished after exclusion of the distal apical segment, which is susceptible to spillover artefacts. An excellent correlation between MBF values was found for global ($r = 0.96$) and regional MBF ($r > 0.94$ for all).

Conclusion
For global and regional MBF, Carimas and Cardiac VUer showed excellent agreement and intra-observer reproducibility. These results confirm that, for patients with intermediate likelihood of CAD, these validated SP are interchangeable and can be utilized for routine clinical practice of $^{15}$O-water cardiac PET.

Keywords
$^{15}$O-water • Software reproducibility • Myocardial perfusion imaging • Coronary artery disease • Myocardial blood flow

Introduction
Non-invasive myocardial perfusion imaging (MPI) is widely used for the diagnostic evaluation of patients with known or suspected coronary artery disease (CAD). Conventional qualitative imaging approaches are based on visual estimates of relative perfusion, which relies on the presence of a reference area with normal myocardial perfusion. This hampers its diagnostic accuracy in patients with multi-vessel disease and/or microvascular dysfunction. Quantitative myocardial perfusion measurements may therefore increase...
diagnostic accuracy. Cardiac positron emission tomography (PET) is the established technique to non-invasively quantify myocardial perfusion in vivo. For this purpose, several tracers have been developed and validated. Of these flow tracers, $^{15}$O-water is considered the gold standard as it is freely diffusible and metabolically inert and therefore, all observed changes in radioactivity concentrations are solely dependent on blood flow. Nonetheless, until recently $^{15}$O-water was not utilized in clinical practice due to the need for onsite tracer production, elaborate post-processing procedures, and the fact that the low signal gradient between myocardium and blood yielded clinically uninterpretable images.

In recent years, however, the exponential growth in PET/CT facilities worldwide has been paralleled by both hardware and software developments that now enable automated generation of myocardial perfusion images with routine quantification of myocardial blood flow (MBF). Two non-commercial clinical tools, Carimas and Caridar, developed by university hospitals, have clinically been well validated in a comparison with invasive measures, and implementation in clinical cardiology is now feasible. Studies that have evaluated these tools, however, have revealed some discrepancies in optimal cut-off values to detect obstructive CAD. These software solutions are based on a single-compartment model as described by lida et al., yet differences exist in definitions of arterial input function, delineation of the myocardial wall, and spillover corrections between blood and tissue compartments. Impact of these differences on obtained MBF values is unknown. Therefore, comparison between these recently developed quantitative myocardial perfusion tools is warranted before the widespread application of $^{15}$O-water PET can be advocated in clinical cardiology.

The current study was therefore conducted to compare two clinically used software packages Carimas and Cardiac VUer.

Materials and methods

Patients population

Data were obtained retrospectively from two comparable cohorts of symptomatic patients (in terms of age and gender distribution), who were clinically evaluated for CAD and therefore referred for MBF measurements. The first cohort (VUmc) consisted of a total of 50 randomly selected patients (32 men, age range 39–78 years, mean age 58 ± 12 year; 18 women, age range 39–78 year, mean age 59 ± 11 year). These patients were scanned at the VU university medical centre. The second cohort (Turku) also consisted of 50 randomly selected patients (32 men, age range 52–74 year, mean age 63 ± 6 year; 18 women, age range 51–74 year, mean age 64 ± 7 year), who were examined at the Turku PET Centre. None of the patients had a documented history of CAD. All the patients had an intermediate risk of CAD based on the Diamond and Forrester criteria. Electrocardiography did not show signs of a previous myocardial infarction, and echocardiography showed a normal left ventricular function without wall motion abnormalities in all patients. Data were in part selected from previously published cohorts.

Written informed consent was obtained in patients who participated in a prospective validation study. In the remaining subjects, the institutional review board approved this retrospective study and the requirement to obtain informed consent was waived.

Image acquisition

Scans from VUmc were performed on a Gemini TF 64 PET-CT (Philips Healthcare, Best, The Netherlands) at the VU university medical centre (Amsterdam, the Netherlands). A 5 mL bolus injection of 370 MBq $^{15}$O-water, followed by 35 mL saline (total duration 23 s), was administered simultaneously with the start of a list-mode emission scan of 6 min in the 3D mode. A slow, respiration averaged low-dose CT scan (LD-CT, 55 mAs, 120 kV, acquiring 20 cm in 12 s compared with <5 s for a regular LD-CT) was performed after each emission scan to correct for photon attenuation and scatter. The emission scan was reconstructed into 22 frames (1 × 10, 8 × 5, 4 × 10, 2 × 15, 13 × 20, 2 × 30, and 2 × 60 s), using the standard (non-time of flight) 3D-RAMLA reconstruction algorithm. Two $^{15}$O-water scans were performed sequentially: one under adenosine-induced stress conditions followed by one under rest conditions after a 10 min delay to allow for decay of radioactivity. Intra-venous adenosine infusion (140 μg kg$^{-1}$ min$^{-1}$) was started 2 min prior to injection of $^{15}$O-water and was terminated after the LD-CT, following the stress scan was performed, to ensure similar circumstances during the stress $^{15}$O-water scan and its corresponding LD-CT.

Scans from Turku were performed using on a hybrid 64-row Discovery VCT PET/CT scanner (General Electrics, W1, USA) at the Turku PET Centre (Turku, Finland). $^{15}$O-water (900–1100 MBq) was injected (Radiowater Generator, Hidex Oy, Turku, Finland) at rest as an i.v. bolus over 15 s at an infusion rate of 10 mL/min. Dynamic acquisition of 4 min 40 s was performed (14 × 5, 3 × 10, 3 × 20, and 4 × 30 s) in the 2D mode. After a 10 min delay following the first injection, a stress

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of utilized software packages</th>
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<tbody>
<tr>
<td></td>
<td>Carimas$^6$</td>
</tr>
<tr>
<td>Model</td>
<td>One-tissue model with PTF$^5$</td>
</tr>
<tr>
<td>Input function</td>
<td>Cylinder in left ventricular cavity</td>
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<tr>
<td>Spillover corrections in model</td>
<td>From left ventricular cavity in myocardium</td>
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<td>ROI definition</td>
<td>On digital subtraction images</td>
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<tr>
<td>Miscellaneous</td>
<td>Automatic with manual adjustment</td>
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<td></td>
<td>Additional parametric images of viability (perfusion tissue index$^{37}$)</td>
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PTF, perfusable tissue fraction.
Figure 1 User interface of Carimas showing the results of a rest (left) and stress (right) scan of a patient with a stress perfusion defect in the LAD territory. The same colour scale was used for both rest and stress (ranging from zero to 3.0 mL min$^{-1}$ g$^{-1}$). The tables list MBF values (F), left ventricular spillover fractions (Va), and perfusable tissue fractions (PTF). The colour bar adjacent to the polar map provides absolute flow values. Note that parts of the basal anteroseptal and inferoseptal segments are excluded from analysis to avoid inclusion of the left ventricular outflow tract. Detailed description of Carimas is given elsewhere.6
Figure 2 User interface of Cardiac VUer of the same patient as in Figure 1. The left panel displays parametric myocardial blood flow (MBF) images in a short axis (upper four rows), vertical long axis (middle two rows), and horizontal long axis (bottom two rows) view. Resting images are displayed inferior to the stress images and colour scales were set from 0 mL min$^{-1}$ g$^{-1}$ to the maximum of rest and stress and are shown in the interface. The right panel shows parametric polar maps for rest and stress as well as coronary flow reserve (CFR), including a table that lists MBF and CFR values. Please note that absolute flow values are given in the adjustable colour bars adjacent to the parametric images. Detailed description of Cardiac VUer is given elsewhere.\textsuperscript{5}
scan was performed during adenosine-induced hyperaemia (140 μg kg⁻¹ min⁻¹). Adenosine was started 2 min before the scan start and continued throughout the dynamic frame acquisition. To correct, for photon attenuation and scatter, a single LD-CT (80 mAs, 120 kV) was performed.

**Data analysis**

Quantitative MBF were obtained using two previously published software packages: Carimas⁵ and Cardiac VUer.⁶ Although some differences in implementation exist, both packages extract the arterial input function directly from the dynamic PET data, use an one-tissue compartment model with a correction for perfusable tissue fraction (PTF) for the estimation of MBF, and define myocardial segments according to the 17 segment model of the American Heart Association.¹³ An overview of the important similarities and differences between Carimas and Cardiac VUer is listed in Table 1. A more detailed description of the exact MBF quantification procedure for these packages can be found in elsewhere.⁵,⁶

All data were analysed by a single observer without prior experience in either software package or who was blinded to the clinical results of all patients. This observer was not involved in any phase of the development of either software package. The observer received a demonstration from the developers of each package and was given a small number of data sets (not included in this study) to become familiar with the software. After this brief training period, the VUer cohort was analysed first. Scans were analysed in a random order for both Carimas and Cardiac VUer separately, although for any patient, stress and rest data were analysed in the same analysis session. To avoid any biases introduced due to a learning curve, the packages were switched after every fifth analysis. After a 2-week intermission where the observer refrained from analyses, this process was repeated. After another 2-week intermission period, this analysis schedule was subsequently applied to the scans of the Turku cohort. In this manner, each scan from each institute was analysed twice by the single observer.

MBF was analysed for the entire LV and for each of the three coronary territories (¹³) (LAD, left anterior descending artery; RCA, right coronary artery; LCx, left circumflex). Reported MBF values were averaged over the two separately conducted analyses of each patient by the single observer. Coronary flow reserve (CFR) was defined as the ratio of stress to rest MBF and calculated for the entire LV and for each of the three coronary territories. Reproducibility of each software package for the entire LV and each of the coronary territories was slightly higher than with Cardiac VUer (2.73 ± 0.82 and 2.63 ± 0.84 mL min⁻¹ g⁻¹, respectively, P = 0.01). CFR was comparable between software packages (2.78 ± 0.87 and 2.73 ± 0.87, respectively, P = 0.27). Mean differences between Carimas and Cardiac VUer are shown in Table 3.

Figure 4 shows the correlation between global MBF values. There was a high and significant correlation between MBF values obtained with either package (r = 0.963, P < 0.001). Bland–Altman analysis displayed a mean difference of −0.06, which was not statistically different from zero (95% confidence interval −0.61 to 0.49 mL min⁻¹ g⁻¹). Likewise, correlation for CFR was high (r = 0.851, P < 0.001). Bland–Altman analysis displayed a mean difference of −0.06, which was not statistically different from zero (95% confidence interval −0.98 to 0.87).

**Regional analysis**

When analysis was conducted at a regional level, as illustrated in Figure 3, rest MBF for the LAD territory as obtained with Carimas was slightly higher than with Cardiac VUer, while for the other territories, Carimas produced slightly lower values, even though all differences were small (1.11 ± 0.32 and 1.00 ± 0.22 mL min⁻¹ g⁻¹ for LAD, respectively, P < 0.001; 0.90 ± 0.27 and 0.96 ± 0.26 mL min⁻¹ g⁻¹ for RCA, respectively, P < 0.001; 1.00 ± 0.26 and 1.03 ± 0.26 mL min⁻¹ g⁻¹ for LCx, respectively, P = 0.01). Stress MBF in the LAD territory for Carimas was statistically and significantly higher, whereas there were no significant differences for the other coronary territories (2.73 ± 0.84 and 2.55 ± 0.80 mL min⁻¹ g⁻¹ for LAD, respectively, P < 0.001; 2.62 ± 0.80 and 2.64 ± 0.91 mL min⁻¹ g⁻¹ for RCA, respectively, P = 0.65; 2.68 ± 0.84 and 2.77 ± 0.96 mL min⁻¹ g⁻¹ for LCx, respectively, P = 0.05). CFR was higher for Carimas only for the RCA territory and there were no significant differences for the LAD and LCx territories (2.57 ± 0.84 and 2.63 ± 0.80 for LAD, respectively, P = 0.26; 3.10 ± 1.12 and 2.84 ± 0.97 for RCA, respectively, P < 0.001; 2.78 ± 0.90 and 2.80 ± 1.03 for LCx, respectively, P = 0.77). An overview of the mean differences can be seen in Table 3.

MBF correlations were also significant for the three vascular territories (Figure 5). CFR correlations per vascular territory were lower when compared with MBF (r = 0.805, r = 0.839, r = 0.834 for LAD, RCA, and LCx, respectively, all P < 0.001). In addition, Bland–Altman analysis showed a high and significant correlation for global MBF values obtained with either package (r = 0.961, P = 0.001). Bland–Altman analysis displayed a mean difference of −0.06, which was not statistically different from zero (95% confidence interval −0.61 to 0.49 mL min⁻¹ g⁻¹). Likewise, correlation for CFR was high (r = 0.851, P < 0.001). Bland–Altman analysis displayed a mean difference of −0.06, which was not statistically different from zero (95% confidence interval −0.98 to 0.87).

### Table 2 Patient characteristics (n = 100)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>64/36</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 ± 10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.0 ± 15.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.5 ± 4.1</td>
</tr>
<tr>
<td>Risk factors for CAD</td>
<td></td>
</tr>
<tr>
<td>Increased family risk</td>
<td>34</td>
</tr>
<tr>
<td>Smoking</td>
<td>40</td>
</tr>
<tr>
<td>Hypertension</td>
<td>51</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13 (all type 2)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>56</td>
</tr>
</tbody>
</table>

**Results**

Figure 1 (Carimas) and Figure 2 (Cardiac VUer) display examples of the user interfaces of the software packages. Both interfaces allow for a comprehensive reading of both qualitative and quantitative nature in the evaluation of perfusion for an individual patient. An overview of patient characteristics can be found in Table 2.

**Global analysis**

The average MBF for both rest and stress obtained with each software package for the entire LV and each of the coronary territories separately is given in Figure 3. Global rest MBF was not significantly different as obtained with Carimas or Cardiac VUer (1.02 ± 0.28 and 0.99 ± 0.23 mL min⁻¹ g⁻¹, respectively, P = 0.07). For stress, Carimas produced slightly but significantly higher values than Cardiac VUer (2.73 ± 0.82 and 2.63 ± 0.84 mL min⁻¹ g⁻¹, respectively, P = 0.01). CFR was comparable between software packages (2.78 ± 0.87 and 2.73 ± 0.87, respectively, P = 0.27). Mean differences between Carimas and Cardiac VUer are shown in Table 3.
analysis displayed a mean difference that was not significantly different from zero for all territories for both CFR and MBF.

### Apical segment

As depicted in Figure 6, the distal apical segment (no. 17) generally produces relative augmented flow values in relation to the rest of the myocardium. To circumvent this issue, Carimas incorporates an additional analysis for the LAD region excluding the distal apical segment (LADwa). The agreement between packages for the LAD territory slightly improved by omission of this segment (LADwa). The agreement between packages for the LAD region excluding the distal apical segment (LADwa). The agreement between packages for the LAD territory slightly improved by omission of this segment (LADwa). The agreement between packages for the LAD region excluding the distal apical segment (LADwa). The agreement between packages for the LAD territory slightly improved by omission of this segment (LADwa). The agreement between packages for the LAD region excluding the distal apical segment (LADwa). The agreement between packages for the LAD territory slightly improved by omission of this segment (LADwa). The agreement between packages for the LAD region excluding the distal apical segment (LADwa). The agreement between packages for the LAD territory slightly improved by omission of this segment (LADwa). The agreement between packages for the LAD region excluding the distal apical segment (LADwa). The agreement between packages for the LAD territory slightly improved by omission of this segment (LADwa).

### Software reproducibility

Intra-observer ICCs are shown in Table 4. Software reproducibility was excellent for both software packages (as indicated by ICCs >0.90).

### Comparison of MBF between patient cohorts

There was no significant difference in average global MBF during rest and stress for patients scanned in either institute for both software packages (P > 0.50 for all). Regional analysis revealed no significant differences in resting or hyperaemic MBF for the RCA and LCx vascular territories between software packages and institutes (P > 0.25 for all). For rest MBF of the LAD territory, a significant difference was found between patients from Vumc and Turku when data were analysed using Carimas (MBF of 1.16 ± 0.33 and 1.03 ± 0.31 mL min⁻¹ g⁻¹, respectively, P = 0.04). This difference was not observed when data were analysed using Cardiac Vuer (MBF of 1.00 ± 0.25 and 0.98 ± 0.20 mL min⁻¹ g⁻¹, respectively, P = 0.81), nor when the distal apical segment was omitted (MBF of 1.01 ± 0.25 and 0.93 ± 0.27 mL min⁻¹ g⁻¹, respectively, P = 0.13). For hyperaemic MBF, no significant differences were documented for the LAD territory between institutes for both software packages (P = 0.84 for Carimas, P = 0.72 for Cardiac Vuer).

### Discussion

The use of absolute, quantitative MBF in clinical practice has gained interest to enhance the diagnostic accuracy for CAD.¹² For quantitative MBF to become a reliable clinical tool, values should be similar, independent of the type of scanner, analysis software, or tracer used, such that standardized cut-off values can be defined to distinguish between normal and ischaemic myocardium. The present study was conducted to evaluate the reproducibility of quantitative MBF analysis when using different non-commercial validated SP, Carimas⁶ and Cardiac Vuer,⁵ using data acquired with ¹⁵O-water at two centres with two types of PET/CT scanners. Although the underlying modelling procedures are similar, differences in implementations may exist in definition of the arterial input function, spillover corrections, and automatic definition of myocardial segments.
All of these factors could, to some extent, influence the generated flow values. However, despite these differences in implementations, an excellent agreement within and between SP was documented in this study. Intra-observer reproducibility was found to be excellent for global and regional MBF for each SP with ICC values of 0.90 and higher. It should be emphasized that a novice operator, with basic cardiac anatomy knowledge, analysed the scans after just a brief training period. This training level proved to be sufficient to ensure high reproducibility of results. Previous studies pertaining these SP have likewise documented that interobserver variability is equally low.6,14 These findings have important clinical implications, as they demonstrate that personnel with brief training can fulfil the task to generate reliable perfusion images upon which clinical decision-making is based. Moreover, post-processing time is in the order of minutes per scan and workload for staff is therefore low, which facilitates high patient throughput and allows rapid grading of (quantitative) MBF images.

Global MBF was comparable between SP and excellent agreement in regional values obtained with either package was observed. However, despite this excellent agreement, minute discrepancies were observed at a regional level of some vascular territories. Nonetheless, these differences reached statistical significance due to the large sample size and paired analysis of the data. In addition, some minor differences in exact definition of the myocardial segments may introduce small differences in obtained MBF values. This is especially pronounced for the most distal apex as the largest differences were found for the LAD territory. For hyperaemia, only the LAD territory displayed slightly higher flow values with Carimas, which also resulted in augmented global values. For both rest and hyperaemic MBF in the LAD territory, this difference was abolished when LAD without the most distal apex was considered in the Carimas SP. For CFR, only the RCA territory yielded some higher values using Carimas.

These observed slight disparities in (stress) MBF and CFR, however, are not likely to be of any clinical impact as reported ischaemic threshold values of PET studies using various tracers (i.e. 82Rb, 13N-ammonia, and 15O-water) for hyperaemic MBF and CFR range from 0.91 to 2.50 mL min\(^{-1}\) g\(^{-1}\) and 1.44–2.74, respectively.6,7,8,15,16,17,18,19,20 When focusing on 15O-water studies, the documented optimal hyperaemic threshold ranges from 1.86 to 2.50 mL min\(^{-1}\) g\(^{-1}\).6,7,8 Also, repeat MBF measures with 15O-water PET display test–retest variability of \(~10–15\%\),21,22 exceeding those observed in the current software comparison study. The
documented inter-software (and observer) variability can thus be considered negligible in relation to such clinical variability to diagnose significant CAD.

Similar to the aforementioned agreement of average MBF data, correlations for MBF at a global and regional scale were excellent and characterized by $r$-values of 0.94 and higher. Furthermore, slopes of the fits were close to unity and intercepts close to zero, indicating that results obtained with either package are interchangeable. It should be noted that for the LAD territory, slope of the correlation was significantly different from unity (0.89) as flow values increasingly diverged at higher flow rates between SP. This observation could be ascribed to augmented perfusion of the most distal apical segment. The latter is not likely to represent a physiological phenomenon but is related to the fact that this small anatomical segment is susceptible to artefacts due to high spillover fractions from adjacent tissue and blood pool and due to patient
and cardiac motion. Accordingly, when this segment was disregarded when using the Carimas SP, differences were no longer apparent and slope of the correlation approached unity (0.99), which was in line with results for other vascular territories. Correlations for CFR were generally governed by slightly more scatter as compared with absolute MBF. This pattern is not unanticipated as the combination of two measurements as a ratio by default introduces larger margins of error. As a consequence, CFR should be considered less reliable in terms of reproducibility between packages when compared with MBF alone. As recent studies have revealed that hyperaemic MBF is of comparable or even superior diagnostic accuracy than CFR, these results further support the use of absolute flow quantification to evaluated CAD and may facilitate stress only by protocols.7,16,17

**Figure 6** Screenshot of a stress scan with augmented apical flow as observed with Carimas (A), which is less apparent with Cardiac Vuer (B).

**Figure 7** Correlation (A) and Bland–Altman (B) plots of MBF in the territory of the left anterior descending artery, without the apex, obtained using Carimas (x-axis) and Cardiac Vuer (y-axis). Black dots represent Vumc data while open circles represent Turku data. Continuous lines denote linear fit in (A) and mean difference in (B) while dashed lines represent 95% confidence intervals in (B). SEE, standard error of the estimate. RPC, repeatability coefficient.

<table>
<thead>
<tr>
<th>ICC</th>
<th>Carimas</th>
<th>Cardiac Vuer</th>
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<tbody>
<tr>
<td>Global</td>
<td>0.967</td>
<td>0.994</td>
</tr>
<tr>
<td>LAD</td>
<td>0.903</td>
<td>0.990</td>
</tr>
<tr>
<td>RCA</td>
<td>0.956</td>
<td>0.993</td>
</tr>
<tr>
<td>LCx</td>
<td>0.955</td>
<td>0.994</td>
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</table>

**Table 4** Intraclass correlation coefficients (ICC) of intra-observer reproducibility

For the entire LV and for each coronary territory, intra-observer reproducibility was excellent (>0.90) for both Carimas and Cardiac Vuer.
Although this study did not aim to compare PET/CT systems from different vendors or to compare different scanning protocols, MBF levels were similar between institutes. This is in line with a previously published multicentre trial, comparing different PET systems and showing that, as long as the scanner has high sensitivity and count rate performance, MBF values are independent of the utilized scanner. Data from this study, however, were obtained with significantly different scanning protocols, especially with respect to scan time (6 and 4 min 40 s) and acquisition mode (3D and 2D). Since, obtained MBF values were not significantly different between both institutes and these differences did not appear to play a major role. This illustrates the consistency of quantitative MBF imaging with 15O-water, irrespective of the scanner or scanning protocol used.

The current study was conducted using in-house developed software from two academic centres with considerable experience in cardiac perfusion imaging using 15O-water PET. This was in part instigated by a paucity of commercial available software, as until recently the use of this perfusion tracer was considered unsuitable for clinical use given the low signal gradient between the blood and the myocardium. Recent advances in software and hardware, however, now enable to produce high quality (quantitative) images using 15O-water as demonstrated by the investigated SP. Although these non-commercial packages are available at no costs, they are not embedded in professional software systems with accompanying commercial support. Quantification software for alternative MBF tracers such as 82Rubidium and 13N-Ammonia is, however, more widely commercially available and therefore have been more convenient for clinical implementation. For both 13N-Ammonia and 82Rubidium, recent data demonstrate that different SP also display high agreement. Studies are ongoing to evaluate the validity of commercial packages to routinely quantify MBF using 15O-water and 82Rubidium PET. Although the software and scanner type for 15O-water PET may be interchangeable, the use of different tracers is not. 15O-water is the only freely diffusible tracer with complete myocardial extraction regardless of flow rate. Extraction of 13N-Ammonia and even more so for 82Rubidium levels off at increasing flow rates, which influences quantification of MBF. As a consequence, normal values and ischaemic thresholds for these tracers are generally reported to be lower when compared with 15O-water. For diagnostic purposes, more prospectively studies are therefore warranted for each tracer individually to establish reliable ischaemic cut-off values.

Of final note, assessment of potential mismatch between the emission and transmission images due to patient motion was not routinely evaluated. As perfusion is estimated from the clearance rate of 15O-water, it is virtually unaffected by potential attenuation artefacts. In fact, it has recently been highlighted that attenuation correction can be omitted altogether for 15O-water MBF studies and patient motion between emission and transmission data has no appreciable influence on estimated MBF. This is in contrast to tracers that employ MBF estimation from the accumulation rate of the tracer.

A limitation of this study is that not all patients were referred for invasive angiography and fraction flow reserve (FFR) measurements, which is considered the gold standard for the evaluation of CAD. Therefore, a direct comparison of results of both SP with those obtained using angiography and FFR could not be conducted in the current study. Further studies with respect to clinical performance of each SP and potential differences in optimal cut-off values to detect obstructive CAD are warranted.

### Conclusion

For global and regional MBF, Carimas and Cardiac Vuer showed excellent agreement and intra-observer reproducibility. These results confirm that, for patients with intermediate likelihood of CAD, these validated SP are interchangeable and can be utilized for routine clinical practice of 15O-water cardiac PET.

### Conflict of interest

H.J.H., A.A.L., and P.K. were involved in development of Cardiac Vuer prior to this study. S.V.N., C.H., and J.K. were involved in development of Carimas prior to this study.

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### References


