Coronary calcium score scans for attenuation correction of quantitative PET/CT (13)N-ammonia myocardial perfusion imaging

Burkhard, N; Herzog, B A; Husmann, L; Pazhenkottil, A P; Burger, I A; Buechel, R R; Valenta, I; Wyss, C A; Kaufmann, P A

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Abstract

PURPOSE: The aim of this study was to evaluate whether ECG-triggered coronary calcium scoring (CCS) scans can be used for attenuation correction (AC) to quantify myocardial blood flow (MBF) and coronary flow reserve (CFR) assessed by PET/CT with (13)N-ammonia. METHODS: Thirty-five consecutive patients underwent a (13)N-ammonia PET/CT scan at rest and during standard adenosine stress. MBF values were calculated using AC maps obtained from the ECG-triggered CCS scan during inspiration and validated against MBF values calculated using standard non-gated transmission scans for AC. CFR was calculated as the ratio of hyperaemic over resting MBF. In all 35 consecutive patients intraobserver variability was assessed by blinded repeat analysis for both AC methods. RESULTS: There was an excellent correlation between CT AC and CCS for global MBF values at rest (n = 35, r = 0.94, p < 0.001) and during stress (n = 35, r = 0.97, p < 0.001) with narrow Bland-Altman (BA) limits of agreement (-0.21 to 0.10 ml/min per g and -0.41 to 0.30 ml/min per g) as well as for global CFR (n = 35, r = 0.96, p < 0.001, BA -0.27 to 0.34). The excellent correlation was preserved on the segmental MBF analysis for both rest and stress (n = 1190, r = 0.93, p < 0.001, BA -0.60 to 0.50) and for CFR (n = 595, r = 0.87, p < 0.001, BA -0.71 to 0.74). In addition, reproducibility proved excellent for global CFR by CT AC (n = 35, r = 0.91, p < 0.001, BA -0.42-0.58) and CCS scans (n = 35, r = 0.94, p < 0.001, BA -0.34-0.45). CONCLUSION: Use of attenuation maps from CCS scans allows accurate quantitative MBF and CFR assessment with (13)N-ammonia PET/CT.
Title: Coronary calcium score scans for attenuation correction of quantitative PET/CT 13N-ammonia myocardial perfusion imaging

Article Type: Original Article

Corresponding Author: Prof. Philipp A Kaufmann, M.D.

Corresponding Author's Institution: University Hospital Zurich

First Author: Nina Burkhard, M.D.

Order of Authors: Nina Burkhard, M.D.; Bernhard A Herzog, M.D.; Lars Husmann, M.D.; Aju P Pazhenkottil, M.D.; Irene A Burger, M.D.; Ronny R Buechel, M.D.; Ines Valenta, M.D.; Christophe A Wyss, M.D.; Philipp A Kaufmann, M.D.

Abstract: Purpose The aim of this study was to evaluate whether ECG-triggered coronary calcium scoring (CCS) scans can be used for attenuation correction (AC) to quantify myocardial blood flow (MBF) and coronary flow reserve (CFR) assessed by PET/CT with 13N-ammonia.

Methods Thirty-five consecutive patients underwent a 13N-ammonia PET/CT scan at rest and during standard adenosine stress. MBF values were calculated using AC-maps obtained from the ECG-triggered CCS scan during inspiration and validated against MBF values calculated using standard non-gated transmission scans for AC. CFR was calculated as ratio of hyperemic over resting MBF. In 15 consecutive patients intraobserver variability was assessed by blinded repeat analysis for both AC methods.

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Response to Reviewers: Reviewer #1:
The authors have adequately addressed all issues. However, one methodological questions remains insufficiently answered:

5. P4: PET and CT Imaging: A tube current of 120mA for the nongated transmission scan seems quite high. What was the reason for that?
Authors' response:
We apologize for this misunderstanding. We have used tube modulation for the transmission scan (30-120mA), not for the CCS scan. We have clarified this issue in the method section.

The transmission scan was nongated. So, on what what was the tube current modulation based then?
Authors:
Thank you for the opportunity to clarify this point. The tube modulation was not based on ECG; it was based on body contour from the scout images. We have clarified this issue in the method section accordingly.
A  Global MBF

<table>
<thead>
<tr>
<th>CCS (ml/min/g)</th>
<th>CT AC (ml/min/g)</th>
</tr>
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<tbody>
<tr>
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<td>5.0</td>
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<tr>
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<tr>
<td>0.0</td>
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</tbody>
</table>

n = 70
r = 0.98
p < 0.001

B  Global CFR

<table>
<thead>
<tr>
<th>CCS</th>
<th>CFR CT AC</th>
</tr>
</thead>
<tbody>
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<td>3.0</td>
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<tr>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>0.0</td>
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</tbody>
</table>

n = 35
r = 0.96
p < 0.001

Difference

Mean: 0.21
Mean: -0.33

Difference

Mean: 0.34
Mean: -0.27
Coronary calcium score scans for attenuation correction of quantitative PET/CT $^{13}$N-ammonia myocardial perfusion imaging

$^{+1}$ Nina Burkhard MD, $^{+1}$ Bernhard A Herzog MD, $^1$Lars Husmann MD, $^1$Aju P. Pazhenkottil MD, $^1$Irene A. Burger, $^1$Ronny R. Buechel MD, $^1$Ines Valenta MD,
$^1$Christophe A. Wyss MD, $^{1,2}$Philipp A Kaufmann MD

$^+$ contributed equally

$^1$Cardiac Imaging, University Hospital Zurich, Switzerland

$^2$Zurich Center for Integrative Human Physiology, University of Zurich, Switzerland

**Corresponding author:** Philipp A. Kaufmann, MD

Professor and Director of Cardiac Imaging

University Hospital Zurich, NUK C42

Ramistrasse 100

CH-8091 Zurich

Switzerland

phone: +41-44-255 4196

tax: +41-44-255 4414

e-mail: pak@usz.ch

**Keywords:**

Attenuation correction, coronary calcium score, PET, myocardial blood flow
Abstract

Purpose The aim of this study was to evaluate whether ECG-triggered coronary calcium scoring (CCS) scans can be used for attenuation correction (AC) to quantify myocardial blood flow (MBF) and coronary flow reserve (CFR) assessed by PET/CT with $^{13}$N-ammonia.

Methods Thirty-five consecutive patients underwent a $^{13}$N-ammonia PET/CT scan at rest and during standard adenosine stress. MBF values were calculated using AC-maps obtained from the ECG-triggered CCS scan during inspiration and validated against MBF values calculated using standard non-gated transmission scans for AC. CFR was calculated as ratio of hyperemic over resting MBF. In 15 consecutive patients intraobserver variability was assessed by blinded repeat analysis for both AC methods.

Results There was an excellent correlation between CT AC and CCS for global MBF values at rest (n=35, r=0.94, P<0.001) and at stress (n=35, r=0.97, P<0.001) with narrow Bland-Altman (BA) limits of agreement (-0.21 to 0.10 ml/min/g and -0.41 to 0.30 ml/min/g), as well as for global CFR (n=35, r=0.96, P<0.001, BA -0.27 to 0.34).

The excellent correlation was preserved on the segmental MBF analysis for both rest and stress (n=1190, r=0.93, P<0.001, BA -0.60 to 0.50), and for CFR (n=595, r=0.87, P<0.001, BA -0.71 to 0.74). In addition, reproducibility proved excellent for global CFR by CT AC (n=15, r=0.98, P<0.001, BA -0.20 to 0.27) and CCS scans (n=15, r=0.94, P<0.001, BA -0.21 to 0.35).

Conclusions Use of attenuation maps from CCS scans allows accurate quantitative MBF and CFR assessment with $^{13}$N-ammonia PET/CT.
Introduction

PET is currently the accepted gold standard for non-invasive myocardial perfusion imaging (MPI) in patients with suspected or known coronary artery disease (CAD). The main advantage of PET over SPECT is its superior spatial resolution and the possibility of non-invasive quantification of the regional myocardial blood flow (MBF) if appropriate tracers [1-5] and adequate attenuation correction (AC) is used. CT images can be transformed into PET attenuation coefficients which allow correction for myocardial perfusion quantification using a hybrid PET/CT scanner [6, 7]. In view of the growing importance of the coronary calcium scoring (CCS) for the non-invasive assessment of CAD and the increasing availability of hybrid PET/CT devices it appears pertinent to evaluate whether multislice CT data from CCS scan obtained on a hybrid scanner, can be used for reliable AC of quantitative MBF from PET/CT and $^{13}$N-ammonia, similar to previous validation for qualitative SPECT MPI [8].

Therefore, the aim of this study was to evaluate whether ECG-triggered CCS scans can be used for AC to quantify MBF and CFR assessed by PET/CT with $^{13}$N-ammonia.
Methods

Study Population

We included 35 consecutive patients (7 females, 28 males) referred for assessment of ischemic heart disease with $^{13}$N-ammonia MPI. Mean age was 65 ± 8.5 years (range: 48 - 84 years) and mean body mass index was 28.4 ± 5.6 kg/m$^2$ (range: 17.1 - 47.9 kg/m$^2$). Thirty participants had angiographically documented CAD and a history of percutaneous coronary revascularization (n = 12), myocardial infarction (n = 19) or previous coronary artery bypass grafting (n = 12). Five patients were evaluated for microvascular disease. The study was approved by the local institutional review board and written informed consent was obtained from the study participants.

PET and CT Imaging

MBF was assessed at rest and standard adenosine-stress (0.14 mg/min/kg of body weight) [9]. Blood pressure and heart rate were recorded every minute and the electrocardiogram was monitored continuously throughout the procedure. Images were acquired either on a Discovery RX (16-Slices CT) or a DVCT (64-Slices CT) (GE Healthcare). First, a CT scout scan was used to localize the field of view for the following CT and emission scans. Transmission data for CT AC were acquired in a non-gated low dose CT scan, using the following parameters: scan length 15 cm, rotation time 0.5 s (16-slice CT) or 0.35 (64-slice CT); tube voltage 140 kV, body contour adapted modulation of tube current (30-120 mA), slice thickness 3.75 mm. CCS scans were performed during inspiration with prospective ECG-triggering using the following parameters: 15 cm, 0.5 s (16-slice CT) or 0.35 (64-slice CT); 140 kV, tube current 400 mA, 2.5 mm. All patients received 750-1000 MBq $^{13}$N-ammonia into a peripheral vein during 10 sec as a slow bolus. Dynamic 3D PET acquisition was
started in parallel and consisted of nine 10 sec, six 15 sec, three 20 sec, two 30 sec, and one 120 sec frames as previously reported [4]. PET data was reconstructed using standard filtered backprojection algorithm with an 8 mm Hanning filter and standard decay scatter sensitivity corrections (voxel size 2.34, 2.34, 3.27). AC was separately performed with CT AC and CCS scans. Quality control included check for misalignment between emission and transmission before reconstruction of PET row data with co registered CT or CCS scan.

Image Processing and MBF

MBF was determined in all patients using the PCARD module of the PMOD software package (version 2.95, PMOD Technologies Ltd, Switzerland) [10-12]. In summary, quantification consisted of the following semi-automatic processing steps: 1) Re-orientation of the images into short axis orientation; 2) Definition of volumes-of-interest in the blood pool of the left (LV) and right ventricle (RV); 3) A 17-segment model of the LV myocardium was used as previously suggested [13]. Average time-activity curves (TAC) were assessed in the LV, the RV, and in each of the 17 myocardial segments (5). Fitting of a 1-tissue compartment model included metabolite correction to the first 4 minutes of the myocardial TACs as well as to the TAC comprising the signal from all segments (average global flow). In addition to the kinetic parameters the model includes factors for geometrical spillover [14] from LV and RV, which were also fitted. The fits resulted in MBF values with units of ml/min/g of myocardial tissue. CFR was calculated as the ratio of hyperemic over resting MBF (relative value) [15]. Segmental results were further grouped into the 3 main coronary territories (left anterior descending, LAD; circumflex artery, CX; and right coronary artery, RCA).
Statistical Analysis

The MBF values at rest and stress are expressed as mean ± standard deviation (SD). Comparison of mean MBF and CFR values obtained by CT AC and CCS scan was performed using paired t-test. Linear regression analysis (Pearson’s correlation coefficient) and Bland-Altman (BA) limits of agreement [16] were used to compare individual values. A P values < 0.05 was considered statistically significant. To assess the intra-observer reproducibility of CT AC as well as CCS scan we blindly reanalysed all $^{13}$N-ammonia PET/CT scans one month apart including realignment of PET and CT. All statistical analyses were performed using a commercially available SPSS software package (SPSS 15.0, SPSS Inc., USA).
Results

Intra-observer variability proved excellent for both, CT AC and CCS for global and segmental MBF (rest and stress) and CFR values (Table 1).

Global MBF values by CCS scan and CT AC compared well at rest (0.96 ± 0.21 vs. 1.02 ± 0.23 ml/min/g, p = ns) and at stress (1.7 ± 0.66 vs. 1.76 ± 0.70 ml/min/g, p=ns), resulting in similar global CFR (1.77 ± 0.59 vs. 1.75 ± 0.60, p = ns) without significant differences documenting an excellent correlation with narrow BA limits of agreement (Table 2). The correlation of global MBF values from both AC methods holds true over a wide range of resting and hyperaemic MBF values (n = 70, r = 0.98, p = ns, BA -0.33 to 0.21 ml/min/g) as reflected by the excellent correlation of global CFR (n=35, r = 0.96, p = ns, BA -0.27 to 0.34) (Fig.1). The excellent correlation was preserved for segmental MBF (n = 1190, r = 0.93, p < 0.001, BA -0.60 to 0.50) and CFR (n = 595, r = 0.87, BA -0.71 to 0.74). Correlation was equally maintained for MBF and CFR after grouping segmental values into the main coronary territories (Table 3). Mean global CCS was 1093 ± 832 (Agatston units) with separate mean values of 555 ± 386 for LAD, 138 ± 164 for CX, and 400 ± 470 for RCA.
Discussion

In the present study we have investigated whether the use of CCS scans for AC of quantitative MPI with $^{13}$N-ammonia PET/CT is feasible. Global and regional MBF and CFR measurements obtained by CCS scan provided results highly comparable to those obtained with conventional CT AC. In addition, this holds true for each of the three coronary vessels underlining the clinical validity. Because of its ability to provide non-invasive regional absolute quantification of MBF [5], MPI with $^{13}$N-ammonia PET/CT has been often used as standard of reference to assess CFR in healthy volunteers and in cardiac patients.

The novelty of the present study is that MPI with PET/CT can provide CCS values on top of quantitative MPI without additional need of an unenhanced CT scan for AC, as the latter can be performed with a CCS scan. The agreement of the quantitative MBF and CFR values for CT AC and CCS and the intra-observer reproducibility observed in our study lies well within the range reported in previous studies using various types of stress such as adenosine [17], bicycle stress [12], dobutamine [18], or cold pressor test [11, 19] and different reconstruction algorithms [20] or tracers [3]. This further strengthens the validity of our results supporting the notion that CCS scans can be used for AC of quantitative MBF assessment by PET MPI. This has clinical implications, because CCS has been established as valuable diagnostic indicator and highly prognostic predictor of cardiovascular events [21]. Recently, CCS has emerged as an important adjunct to SPECT [4] or PET [22] MPI providing diagnostic and prognostic information. In particular, in patients with normal perfusion, some authors have found an added value of high calcium score to discriminate between low and high event rate [22], or to identify CAD [23]. This may mainly apply to patients with intermediate likelihood for CAD, whereas our population may represent a slightly higher likelihood of CAD as a history of CAD was not uncommon.
However, the scope of the present study was to prove the validity of AC by CCS in unselected patients, known CAD was not an exclusion criteria.

Following issues may be seen as limitations of this study. Scanning parameters and reconstruction algorithms are optimized specifically for each camera. Thus, the results obtained from our device may not be entirely generalized to other types of PET scanners. In addition, we did not assess whether differences in the extent of coronary calcification may have an impact on the quality of AC and therefore, may affect MBF values. Unfortunately there is no additional independent standard of reference to verify such interference. However, as this would equally apply to both methods of AC it may not have affected the comparability and interchange ability of both methods. Furthermore, we performed the CCS scan in inspiration following the generally accepted recommendations, although it has been previously reported, that CCS in full expiration may be more accurate for correction in the apical myocardium [4]. However, the latter has been reported for SPECT but not for PET scans. In addition, comparison of CCS in inspiration versus expiration was beyond the scope of the present study. Finally, the prognostic value of CCS may be limited in patients with known CAD, although excellent diagnostic value has been reported for symptomatic patients.

Conclusions

Use of attenuation maps from CCS scans allows accurate quantitative MBF and CFR assessment with $^{13}$N-ammonia PET/CT.

**Acknowledgement**

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Trinckauf, Ennio Mueller, Mirjam De Bloeme, Verena Weichselbaumer and Edlira Loga for their excellent technical support.
References


7. Burger C, Goerres G, Schoenes S, Buck A, Lonn AH, Von Schulthess GK. PET attenuation coefficients from CT images: experimental evaluation of the


Figure legends

Fig. 1:

A) Comparison of global myocardial blood flow (MBF) from coronary calcium scoring (CCS) scans vs. computed tomography attenuation correction (CT AC) reveals excellent correlation (left panel) and narrow Bland-Altman limits of agreement (right panel, dashed lines).

B) Comparison of coronary flow reserve (CFR) from CCS scans vs. CT AC reveals excellent correlation (left panel) and narrow Bland-Altman limits of agreement (right panel, dashed lines).
### Tables

#### Table 1  Intra-observer variability of MBF and CFR

<table>
<thead>
<tr>
<th></th>
<th>CT AC</th>
<th></th>
<th></th>
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<tr>
<td>MBF Rest (n=35)</td>
<td>0.80</td>
<td>&lt;0.001</td>
<td>-0.32</td>
<td>0.23</td>
<td>0.92</td>
<td>&lt;0.001</td>
<td>-0.26</td>
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<td>MBF Stress</td>
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<td>&lt;0.001</td>
<td>-0.54</td>
<td>0.49</td>
<td>0.95</td>
<td>&lt;0.001</td>
<td>-0.46</td>
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<td>CFR</td>
<td>0.91</td>
<td>&lt;0.001</td>
<td>-0.42</td>
<td>0.58</td>
<td>0.94</td>
<td>&lt;0.001</td>
<td>-0.34</td>
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<td>MBF Rest (n=595)</td>
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<td>&lt;0.001</td>
<td>-0.52</td>
<td>0.53</td>
<td>0.80</td>
<td>&lt;0.001</td>
<td>-0.42</td>
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<td>MBF Stress</td>
<td>0.83</td>
<td>&lt;0.001</td>
<td>-0.87</td>
<td>0.87</td>
<td>0.92</td>
<td>&lt;0.001</td>
<td>-0.59</td>
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<td>CFR</td>
<td>0.80</td>
<td>&lt;0.001</td>
<td>1.02</td>
<td>1.04</td>
<td>0.86</td>
<td>&lt;0.001</td>
<td>-0.73</td>
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</table>

MBF myocardial blood flow (ml/min/g), CFR coronary flow reserve (relative units), CT AC computed tomography attenuation correction, CCS coronary calcium score scan, r correlation coefficient, BA Bland-Altman limits of agreement.
### Table 2 Comparison of global MBF and CFR using CT AC and CCS scans (n = 35)

<table>
<thead>
<tr>
<th></th>
<th>CT AC</th>
<th>CCS</th>
<th>difference</th>
<th>p</th>
<th>r</th>
<th>p</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBF Rest</td>
<td>0.96 ± 0.21</td>
<td>1.02 ± 0.23</td>
<td>-0.06 ± 0.08</td>
<td>ns</td>
<td>0.94</td>
<td>&lt;0.001</td>
<td>-0.21 – 0.10</td>
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<td>MBF Stress</td>
<td>1.70 ± 0.66</td>
<td>1.76 ± 0.70</td>
<td>-0.06 ± 0.18</td>
<td>ns</td>
<td>0.97</td>
<td>&lt;0.001</td>
<td>-0.41 – 0.30</td>
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<tr>
<td>CFR</td>
<td>1.77 ± 0.59</td>
<td>1.75 ± 0.60</td>
<td>0.04 ± 0.16</td>
<td>ns</td>
<td>0.96</td>
<td>&lt;0.001</td>
<td>-0.27 – 0.34</td>
</tr>
</tbody>
</table>

MBF myocardial blood flow (ml/min/g), CFR coronary flow reserve (relative units), CT AC computed tomography attenuation correction, CCS coronary calcium score scan, r correlation coefficient, BA Bland-Altman limits of agreement, ns non significant

### Table 3 Comparison MBF and CFR using CT AC and CCS scans (n = 35) in the coronary territories

<table>
<thead>
<tr>
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<th>CT AC</th>
<th>CCS</th>
<th>difference</th>
<th>p</th>
<th>r</th>
<th>p</th>
<th>BA</th>
</tr>
</thead>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>LAD</td>
<td>0.94 ± 0.18</td>
<td>1.01 ± 0.21</td>
<td>-0.07 ± 0.11</td>
<td>ns</td>
<td>0.84</td>
<td>&lt;0.001</td>
<td>-0.29 – 0.14</td>
</tr>
<tr>
<td>CX</td>
<td>1.09 ± 0.32</td>
<td>1.13 ± 0.31</td>
<td>-0.04 ± 0.11</td>
<td>ns</td>
<td>0.94</td>
<td>&lt;0.001</td>
<td>-0.25 – 0.17</td>
</tr>
<tr>
<td>RCA</td>
<td>0.90 ± 0.21</td>
<td>0.93 ± 0.24</td>
<td>-0.03 ± 0.09</td>
<td>ns</td>
<td>0.93</td>
<td>&lt;0.001</td>
<td>-0.20 – 0.14</td>
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<td>Stress</td>
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<tr>
<td>LAD</td>
<td>1.58 ± 0.63</td>
<td>1.68 ± 0.66</td>
<td>-0.08 ± 0.18</td>
<td>ns</td>
<td>0.96</td>
<td>&lt;0.001</td>
<td>-0.44 – 0.24</td>
</tr>
<tr>
<td>CX</td>
<td>1.94 ± 0.73</td>
<td>1.97 ± 0.73</td>
<td>-0.03 ± 0.25</td>
<td>ns</td>
<td>0.94</td>
<td>&lt;0.001</td>
<td>-0.52 – 0.47</td>
</tr>
<tr>
<td>RCA</td>
<td>1.55 ± 0.69</td>
<td>1.58 ± 0.71</td>
<td>-0.03 ± 0.22</td>
<td>ns</td>
<td>0.96</td>
<td>&lt;0.001</td>
<td>-0.44 – 0.38</td>
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<tr>
<td>CFR</td>
<td></td>
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<tr>
<td>LAD</td>
<td>1.70 ± 0.58</td>
<td>1.70 ± 0.63</td>
<td>-0.01 ± 0.18</td>
<td>ns</td>
<td>0.96</td>
<td>&lt;0.001</td>
<td>-0.37 – 0.35</td>
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<tr>
<td>CX</td>
<td>1.90 ± 0.73</td>
<td>1.84 ± 0.67</td>
<td>0.06 ± 0.30</td>
<td>ns</td>
<td>0.91</td>
<td>&lt;0.001</td>
<td>-0.52 – 0.64</td>
</tr>
<tr>
<td>RCA</td>
<td>1.72 ± 0.61</td>
<td>1.71 ± 0.57</td>
<td>0.01 ± 0.20</td>
<td>ns</td>
<td>0.94</td>
<td>&lt;0.001</td>
<td>-0.39 – 0.41</td>
</tr>
</tbody>
</table>

MBF myocardial blood flow (ml/min/g), CFR coronary flow reserve (relative units), CT AC computed tomography attenuation correction, CCS coronary calcium score scan, r correlation coefficient, BA Bland-Altman limits of agreement, LAD left anterior descending artery, CX circumflex artery, RCA right coronary artery, ns non significant