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ORIGINAL ARTICLE

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

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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.

Keywords Attenuation correction · Coronary calcium score · PET · Myocardial blood flow

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) are 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 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 a 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].

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

Methods

Study population

We included 35 consecutive patients (7 women, 28 men) referred for assessment of ischaemic heart disease with ^{13}N-ammonia MPI. The 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 during standard adenosine stress (0.14 mg/min per 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-slice CT) or a DVCT (64-slice 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) and 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 and 2.5 mm. All patients received 750–1,000 MBq ^{13}N-ammonia into a peripheral vein during 10 s as a slow bolus. Dynamic 3-D PET acquisition was started in parallel and consisted of nine 10-s, six 15-s, three 20-s, two 30-s and one 120-s frames as previously reported [4]. PET data were reconstructed using a 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 coregistered 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, Zurich, Switzerland) [10–12]. In summary, quantification consisted of the following semi-automatic processing steps: (1) reorientation 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) and (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 one-tissue compartment model included metabolite correction to the first 4 min 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 per g of myocardial tissue. CFR was calculated as the ratio of hyperaemic over resting MBF (relative value) [15]. Segmental results were further grouped into the three main coronary territories (left anterior descending, LAD; circumflex artery, CX; and right coronary artery, RCA).

Statistical analysis

The MBF values at rest and during 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 the 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 value <0.05 was considered statistically significant. To assess the intraobserver reproducibility of CT AC as well as CCS scan we blindly reanalysed all ^{13}N-ammonia PET/CT scans 1 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., Chicago IL, USA).

Results

Intraobserver 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 per g, p = ns) and during stress (1.7±0.66 vs 1.76±0.70 ml/min per g, p = ns), resulting in similar global CFR (1.77±0.59 vs 1.75±0.60, p = ns) without significant differences document-

Table 1 Intraobserver variability of MBF and CFR

	CT AC			CCS		
	r	*p*	BA	*r*	*p*	BA
Global						
MBF rest (*n*=35)	0.80	<0.001	−0.32–0.23	0.92	<0.001	−0.26–0.24
MBF stress	0.92	<0.001	−0.54–0.49	0.95	<0.001	−0.46–0.44
CFR	0.91	<0.001	−0.42–0.58	0.94	<0.001	−0.34–0.45
Segmental						
MBF rest (*n*=595)	0.80	<0.001	−0.52–0.53	0.80	<0.001	−0.42–0.46
MBF stress	0.83	<0.001	−0.87–0.87	0.92	<0.001	−0.59–0.60
CFR	0.80	<0.001	1.02 −1.04	0.86	<0.001	−0.73–0.68

MBF myocardial blood flow (ml/min per 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

ing 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 per 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=1,190, 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). The mean global CCS was 1,093±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 a 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 for 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 intraobserver 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 a 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, and known CAD was not an exclusion criterion.

The following issues may be seen as limitations of this study. Scanning parameters and reconstruction algorithms

Table 2 Comparison of global MBF and CFR using CT AC and CCS scans (n=35)

	CT AC	CCS	Difference	*p*	*r*	*p*	BA
MBF rest	0.96±0.21	1.02±0.23	−0.06±0.08	ns	0.94	<0.001	−0.21–0.10
MBF stress	1.70±0.66	1.76±0.70	−0.06±0.18	ns	0.97	<0.001	−0.41–0.30
CFR	1.77±0.59	1.75±0.60	0.04±0.16	ns	0.96	<0.001	−0.27–0.34

MBF myocardial blood flow (ml/min per 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

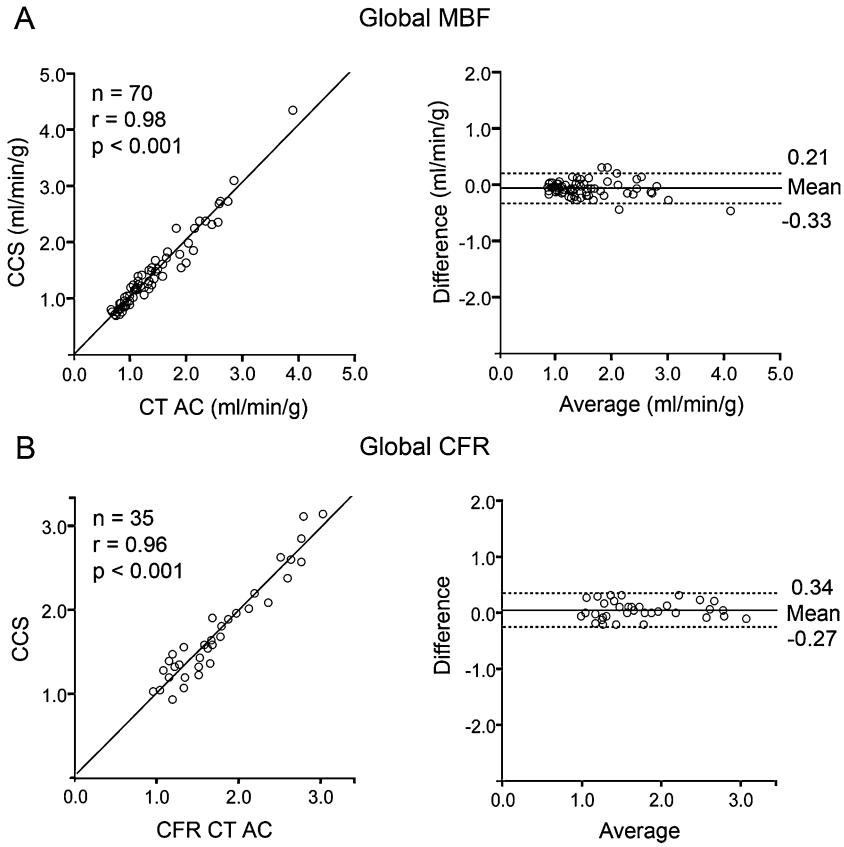

Fig. 1 **a** Comparison of global myocardial blood flow (MBF) from coronary calcium scoring (CCS) scans vs computed tomography attenuation correction (CT AC) reveals excellent correlation (*left panel*) and narrow Bland-Altman limits of agreement (*right panel*, *dashed lines*). **b** Comparison of coronary 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*)

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 an excellent diagnostic value has been reported for symptomatic patients.

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

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

MBF myocardial blood flow (ml/min per 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

Conclusion

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

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References

1. Muzik O, Beanlands RS, Hutchins GD, Mangner TJ, Nguyen N, Schwaiger M. Validation of nitrogen-13-ammonia tracer kinetic model for quantification of myocardial blood flow using PET. J Nucl Med 1993;34:83–91.
2. Okazawa H, Takahashi M, Hata T, Sugimoto K, Kishibe Y, Tsuji T. Quantitative evaluation of myocardial blood flow and ejection fraction with a single dose of (13)NH(3) and gated PET. J Nucl Med 2002;43:999–1005.
3. Nagamachi S, Czernin J, Kim AS, Sun KT, Bottcher M, Phelps ME, et al. Reproducibility of measurements of regional resting and hyperemic myocardial blood flow assessed with PET. J Nucl Med 1996;37:1626–31.
4. Schepis T, Gaemperli O, Treyer V, Valenta I, Burger C, Koepfli P, et al. Absolute quantification of myocardial blood flow with 13N-ammonia and 3-dimensional PET. J Nucl Med 2007;48:1783–9.
5. Kaufmann PA, Camici PG. Myocardial blood flow measurement by PET: technical aspects and clinical applications. J Nucl Med 2005;46:75–88.
6. Koepfli P, Hany TF, Wyss CA, Namdar M, Burger C, Konstantinidis AV, et al. CT attenuation correction for myocardial perfusion quantification using a PET/CT hybrid scanner. J Nucl Med 2004;45:537–42.
7. Burger C, Goerres G, Schoenes S, Buck A, Lonn AH, Von Schulthess GK. PET attenuation coefficients from CT images: experimental evaluation of the transformation of CT into PET 511-keV attenuation coefficients. Eur J Nucl Med Mol Imaging 2002;29:922–7.
8. Schepis T, Gaemperli O, Koepfli P, Rüegg C, Burger C, Leschka S, et al. Use of coronary calcium score scans from stand-alone multislice computed tomography for attenuation correction of myocardial perfusion SPECT. Eur J Nucl Med Mol Imaging 2007;34:11–9.
9. 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.
10. Namdar M, Koepfli P, Grathwohl R, Siegrist PT, Klainguti M, Schepis T, et al. Caffeine decreases exercise-induced myocardial flow reserve. J Am Coll Cardiol 2006;47:405–10.
11. Siegrist PT, Gaemperli O, Koepfli P, Schepis T, Namdar M, Valenta I, et al. Repeatability of cold pressor test-induced flow increase assessed with H(2)(15)O and PET. J Nucl Med 2006;47:1420–6.
12. Wyss CA, Koepfli P, Mikolajczyk K, Burger C, von Schulthess GK, Kaufmann PA. Bicycle exercise stress in PET for assessment of coronary flow reserve: repeatability and comparison with adenosine stress. J Nucl Med 2003;44:146–54.
13. 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;105:539–42.
14. Hutchins GD, Schwaiger M, Rosenspire KC, Krivokapich J, Schelbert H, Kuhl DE. Noninvasive quantification of regional blood flow in the human heart using N-13 ammonia and dynamic positron emission tomographic imaging. J Am Coll Cardiol 1990;15:1032–42.
15. DeGrado TR, Hanson MW, Turkington TG, Delong DM, Brezinski DA, Vallée JP, et al. Estimation of myocardial blood flow for longitudinal studies with 13N-labeled ammonia and positron emission tomography. J Nucl Cardiol 1996;3:494–507.
16. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–10.
17. 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.
18. Jagathesan R, Kaufmann PA, Rosen SD, Rimoldi OE, Turkeimer F, Foale R, et al. Assessment of the long-term reproducibility of baseline and dobutamine-induced myocardial blood flow in patients with stable coronary artery disease. J Nucl Med 2005;46:212–9.
19. Schindler TH, Zhang XL, Prior JO, Cadenas J, Dahlbom M, Sayre J, et al. Assessment of intra- and interobserver reproducibility of rest and cold pressor test-stimulated myocardial blood flow with (13)N-ammonia and PET. Eur J Nucl Med Mol Imaging 2007;34:1178–88.
20. Adachi I, Gaemperli O, Valenta I, Schepis T, Siegrist PT, Treyer V, et al. Assessment of myocardial perfusion by dynamic O-15-labeled water PET imaging: validation of a new fast factor analysis. J Nucl Cardiol 2007;14:698–705.
21. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336–45.
22. Schenker MP, Dorbala S, Hong EC, Rybicki FJ, Hachamovitch R, Kwong RY, et al. Interrelation of coronary calcification, myocardial ischemia, and outcomes in patients with intermediate likelihood of coronary artery disease: a combined positron emission tomography/computed tomography study. Circulation 2008;117:1693–700.
23. Schepis T, Gaemperli O, Koepfli P, Namdar M, Valenta I, Scheffel H, et al. Added value of coronary artery calcium score as an adjunct to gated SPECT for the evaluation of coronary artery disease in an intermediate-risk population. J Nucl Med 2007;48:1424–30.