Adenosine Stress High-pitch 128-slice Dual Source Myocardial Computed Tomography Perfusion For Imaging Of Reversible Myocardial Ischemia: Comparison with Magnetic Resonance Imaging

Feuchtnet et al: Myocardial Perfusion Imaging with CT

1,2,3 Gudrun Feuchtner, MD; 1Robert Goetti, MD; 4André Plass, MD; 4Monika Wieser, MD; 1Hans Scheffel, MD; 5Christophe Wyss, MD; 1Paul Stolzmann, MD; 1Olivio Donati, MD; 3Johannes Schnabl, MD; 4Volkmar Falk, MD; 1Hatem Alkadhi, MD; MPH; 1Sebastian Leschka, MD; 2 Ricardo C. Cury, MD

1Institute of Diagnostic Radiology, University Hospital Zurich, Switzerland
2Baptist Cardiac and Vascular Institute and Baptist Hospital Miami, USA
3Department of Radiology, Innsbruck Medical University, Austria
4Clinic for Cardiovascular Surgery, University Hospital Zurich, Switzerland
5Department of Cardiology, University Hospital Zurich, Switzerland

Correspondence to
Gudrun M. Feuchtner, M.D., Ao.Prof.
Current address: Innsbruck Medical University, Dept. Radiology
Anichstrasse 35
A-6020 Innsbruck, Austria, Europe
Email. Gudrun.Feuchtner@i-med.ac.at
Tel: 0043-512-504-8198
Fax. 0043-512-504-24029

Journal Subject Codes:[30] CT and MRI
Abstract

**Background**—Coronary computed tomography angiography (CTA) enables accurate anatomic evaluation of coronary artery stenosis, however lacking information about hemodynamical significance. The aim of this study was to evaluate 128-slice myocardial CT perfusion (CTP) imaging with adenosine stress using a high-pitch mode, in comparison with cardiac magnetic resonance imaging (CMR).

**Methods and Results**—39 patients with intermediate-to-high coronary risk profile underwent adenosine stress 128-slice dual source CTP (128x0.6mm, 0.28s). Among those, 30 patients (64±10y, 6% females) also underwent adenosine stress CMR (1.5T). The 2-steps CTP protocol consisted of: 1) Adenosine stress-CTP using a high-pitch factor (3.4) ECG-synchronized spiral mode and 2) rest-CTP/coronary-CTA using either high-pitch (HR<63bpm) or prospective ECG-triggering (HR>63bpm). Results were compared to CMR and to invasive angiography (IA) in 25 patients. The performance of stress-CTP for detection of myocardial perfusion defects compared to CMR was: sens. 96%, spec. 88%, PPV 93%, NPV 94% (per vessel), and sens. 78%, spec. 87%, PPV 83%, NPV 84% (per segment). The accuracy of stress-CTP for imaging of reversible ischemia compared to CMR was: sens 95%, spec 96%, PPV 95%, NPV 96% (per vessel). In 25 patients who underwent IA, the accuracy of CTA for detection of stenosis >70% was (per segment): sens. 96%, spec. 88%, PPV 67%, NPV 98.9%. The accuracy improved from 84% to 95% after adding stress CTP to CTA. Radiation exposure of the entire stress/rest CT protocol was only 2.5mSv.

**Conclusions**—Adenosine-induced stress 128-slice dual source high-pitch myocardial CTP allows for simultaneously assessment of reversible myocardial ischemia and coronary stenosis with good diagnostic accuracy as compared to CMR and IA, at a very low radiation exposure.

**Key Words:** adenosine stress myocardial perfusion, CT, CMR, CAD
Multislice coronary computed tomography angiography (CTA) is an accurate tool in the non-invasive work-up of patients with suspected coronary artery disease (CAD). Its strength comprises a high sensitivity in detecting coronary stenosis >50%\textsuperscript{1-3} with an excellent negative predictive value. For clinical use, coronary CTA is recommended in patients with low-to-intermediate pre-test probability of CAD\textsuperscript{4}. However CTA is limited to anatomic grading of coronary stenosis lacking information regarding a stenosis’ hemodynamic significance. This limitation often necessitates additional testing for myocardial ischemia, as coronary revascularization by percutaneous coronary intervention or coronary artery bypass graft (CAGB) surgery is indicated in the presence of ischemia.

Myocardial perfusion imaging (MPI) using either single photon emission tomography (SPECT), positron emission tomography or cardiac magnetic resonance imaging (CMR) are the reference methods for imaging of myocardial ischemia.

The advantage of CMR over myocardial SPECT encompasses a high spatial resolution of \textasciitilde 1-2mm\textsuperscript{5}. Initial data in animals\textsuperscript{6} and humans\textsuperscript{7-9} indicate that myocardial computed tomography perfusion (CTP) enables the detection of myocardial ischemia and infarct\textsuperscript{7-9} with good accuracy as compared to SPECT, at a radiation exposure of \textasciitilde 12.7mSv\textsuperscript{7}.

Recently, a 128-slice dual-source CT (DSCT) system was introduced, providing a spatial resolution of \textasciitilde 0.3-0.4mm\textsuperscript{3}, improved temporal resolution of 75ms, and a new prospective ECG-synchronized high-pitch spiral mode allowing for fast image acquisition within less than 0.4 seconds, at a low radiation dose of \textasciitilde 1mSv\textsuperscript{10-11}. The advantage of cardiac CT is complementary evaluation of coronary arteries and myocardial perfusion, permitting the visualization of both coronary anatomy and physiology.
Therefore, the primary aim of our study was to evaluate the accuracy of adenosine stress 128-slice high-pitch CTP for assessment of myocardial perfusion including the detection of reversible myocardial ischemia or infarction, as compared to CMR. Secondary aim was to compare coronary CTA as part of a comprehensive stress CT protocol with invasive angiography (IA).

Methods

Study population and design

This prospective study was approved by local ethics committee. Each participating subject gave written informed consent. Patients with an intermediate-to-high coronary risk profile were prospectively enrolled.

Inclusion criteria

The CT and CMR examinations were performed on the same day. Patients were recruited if they had suspected or known CAD, and were able to sign informed consent. Patients were advised to stop caffeine intake for at least 12 hours before the study. No beta-blockers or nitroglycerine pre-medication were given prior. Metformin was discontinued for at least 48 hours. A 12-lead ECG was taken. The creatinine was determined. In patients in whom CTP and coronary CTA was directly compared with invasive angiography (IA), the time interval between CT and IA was maximal 6 weeks.

Exclusion criteria

Severe aortic stenosis, long QT syndrome (heart rate corrected QT >440ms), AV-Block grade II/III, sick-sinus-syndrome, heart failure NYHA III/IV, left ventricular ejection fraction<30%, renal dysfunction (creatinine>110 μmol/l, GFR <60ml/min/1.73m²), severe left
main stenosis, chronic obstructive pulmonary disease, asthma, acute coronary syndrome (ACS) within <48 hours, unstable angina, atrial fibrillation.

During adenosine injection, the patients ECG, heart rate, blood pressure and symptoms were monitored. Adenosine injection was stopped if a cessation criterion occurred. Cessation criteria were: severe chest pain, drop in blood pressure >40mmHg, ECG-signs of arrhythmia and new onset of ST-segment depression or elevation.

**Cardiac CT exam**

A 128-slice dual source CT system was used (*Somatom Definition Flash, Siemens Healthcare, Germany*). In each patient, two intravenous cannulas (one on each side) were placed. Baseline HR and systolic and diastolic blood pressure (BP) during adenosine injection were noted at 30 seconds, 2 min and after completing injection.

The CT scan protocol consisted of 2-steps (*Figure 1*). First, stress-myocardial CTP was performed. Adenosine was injected intravenously with an infusion pump at a dosage of 140mcg/kg/min for 3 minutes, at which point the stress CTP scan was initiated. Adenosine injection continued during the CT exam. For stress CTP, a bolus of 60cc non-ionic iodine contrast agent with 370 mg/mL iodine concentration (iopromide, Ultravist 370™, Bayer Schering, Germany) was injected using an injector (Medtron™, Germany) at a flow rate of 5 cc/s followed by 60 cc mixed contrast agent/saline solution (20%/80%). The CT scan was triggered using “bolus tracking technique”, after 100 Hounsfield Units (HU) were reached in the ascending aorta. Patients were holding breath at mid-inspiration. The scan length extended from the pulmonary artery bifurcation to the apex of the heart. Prospective ECG-synchronization was applied. The scan start was triggered at 60% of the RR-interval, resulting in end-diastolic image acquisition from 60 to 80%. Scan parameters were: slice acquisition 2x128x0.6 mm, gantry
rotation time 280 ms, tube potential 100 kilovoltage (kV) if body mass index (BMI) of <30 kg/m², and 120kV if BMI was >30 kg/m². Tube current–time product was set at 320 mAs/rotation. Pitch factor was 3.4.

Second, after a delay of at least 5 minutes, rest myocardial CTP/coronary CTA (Figure 1) was performed using a second iodine contrast bolus injection with the same contrast bolus volume of 60 cc and flow rate as for stress CT. Identical scan parameters as described for the stress CT were used. High-pitch mode (pitch, 3.4) was applied if HR was <63 bpm, or prospective ECG-triggering (“dual-step pulsing”)¹² was performed if HR was >63 bpm.

Automated computed tomography dose index (CTDIvol), dose-length-product (DLP) and effective dose calculated as DLP x c (conversion factor, 0.014)¹³ were collected.

CT images were reconstructed at 0.75mm slice width (increment=0.5) and with a medium-to-smooth image reconstruction kernel. CT images were transferred to a workstation (LeonardoTM,Siemens). Short axis views of the left ventricle (LV) were generated from 4- and 2-chamber views in thick average (5mm slice width, multiplanar reformation (MPR). Two independent reviewers (with 7 years and 9 months of experience) performed myocardial CTP readouts independently and blinded. Reader 1 repeated readouts after 6 weeks. The latter consensus was used.

Left ventricular (LV)-myocardium was evaluated using 16-segment AHA model¹⁴ for the presence of hypoattenuating perfusion defects during stress and rest. The type of myocardial perfusion defects was defined as completely reversible (CR) if present only during stress CTP; partially reversible (PR) larger on stress CTP as compared to rest-CTP and fixed (FD) if similar size was seen during stress and rest-CTP. Segments with fixed defects were regarded as myocardial infarctions. Additionally, segments with myocardial thinning of ≤5mm thickness were defined as infarctions.
A 4-point-score was given for each myocardial segment regarding the diagnostic confidence of perfusion defect evaluation based on image quality (4=very uncertain: poor confidence, could be artefact or poor image quality; 3=uncertain, moderate confidence, rather artefact and less likely a perfusion defect; 2=rather certain: good confidence, probably defect, good image quality/no or minor artifacts, 1=very certain, excellent image quality/no artifacts).

Coronary CTA datasets during rest were reviewed for the presence of coronary stenosis>70% per-segment using the modified AHA-16-segment classification\textsuperscript{15} by one experienced observer. Coronary stents were included.

**Cardiac Magnetic Resonance Imaging**

Cardiac MR exams were performed on a 1.5 Tesla unit (Philips Achieva, Best, Netherlands) using a 5-element cardiac phased-array receiver coil and during breath hold in end-inspiration.

A stack of short axis steady-state free precession slices of the LV myocardium were generated from a series of scout images. Three representative short-axis sections were obtained, one each in the basal, mid-ventricular and apical region for perfusion MRI.

For stress MR perfusion imaging, adenosine was injected intravenously at 140 μg/kg during a minimum of 2.5min and continued during the exam. Sequences were acquired immediately following Gadoterate meglumine (Gd-DOTA) (Dotarem; Guerbet Research, Aulnay-sous-Bois, France) injection (concentration=0.1mmol/kg) using an automated injector (MR Spectris; Medrad, Pittsburgh, PA) (flow rate, 5cc/s and 40cc saline flush). Heart rate and blood pressure were noted before, after 30 seconds and after 2min of adenosine injection (as in the CT study).
MR rest perfusion was performed 10 minutes after stress, using the same sequence and image orientation, and a second bolus of 0.1 mmol Gd-DOTA. SENSE (k-t sensitivity encoding) imaging was used with a saturation recovery gradient-echo pulse sequence for both of these sequences (repetition time/echo time 3.1/1.1 ms, flip angle 20°, saturation prepulse delay 110 ms, partial Fourier sampling, acquisition window 120 ms, section thickness 10 mm, k-t factor of 5 with 11 k-t interleaved training profiles, effective acceleration 3.7, three sections acquired sequentially during a single R–R interval), providing an in-plane resolution of ~1.25×1.25 mm.

Delayed enhancement (DE) was performed in a continuous short-axis view using an inversion-recovery gradient-recalled echo MR sequence (field-of-view 350–400 mm, repetition time/echo time 7.4/4.3 ms, inversion time 200–350 ms, flip angle 20°, matrix 240×240, slice thickness 10 mm). The inversion time was chosen individually according to a Look-Locker sequence to optimize myocardial nulling.

CMR readouts were performed by 2 independent observers (8 and 3 years experience). Consensus was applied. Rest and stress were evaluated for myocardial perfusion defects according to the modified 17-segment AHA model14 (minus the apical segment). The DE sequences were evaluated for delayed hyper-enhancement, consistent with irreversible myocardial injury.

Confidence scores were given for all sequences as follows: 4=very uncertain and/or poor image quality due to artifacts (e.g.respiratory movements), 3=uncertain and/or moderate image quality, 2=probably certain and/or minor image quality limitations, 1=certain/excellent image quality. Myocardial territories were assigned to the three major coronary arteries.14
Invasive Angiography (IA)

Invasive coronary angiography was performed on average in seven projections (four views of the left and three views of the right coronary artery). Quantitative coronary angiography (QCA) was performed. Hemodynamically significant coronary stenosis was considered present if there was 70% or more luminal narrowing, as depicted with coronary angiography.

Statistical analysis

Statistical analysis was performed using SSPS Software (SSPS, Version 14, Chicago, IL). Quantitative data are expressed as mean±standard deviation. For comparison of CTP with CMR, the sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were calculated. Receiver operating curve (ROC) analysis and the area under the curve (AUC) were calculated. The intraclass correlation coefficient (ICC) was calculated to express intra-individual variations and interpreted as: 0-0.2 indicates poor, 0.3-0.4 fair, 0.5-0.6 moderate, 0.7-0.8 strong and >0.8 almost perfect agreement. A generalized estimating equation (GEE) was performed to test for independency among myocardial segments and vessel territories for both the “reversible” and “all-defect” analysis. A p-value of more than >0.05 was regarded as criterion to rule out correlation and to proof independency. Quasi Likelihood under Independence Model Criterion (QIC) was applied to determine “goodness of fit” of GEE. A hierarchic linear model is presented for vessel-based-analysis, variance was calculated and p<0.05 was regarded as significant.
For inter- and intraobserver variability, Cohen’s kappa value was applied.

The diagnostic accuracy of CTP compared to invasive angiography for detection of stenosis >70% was calculated per vessel, and those of CTA per-vessel (LAD, LCX, RCA) and per segment (n=16).

The accuracy of using combined CTP/CTA for detection of >70% stenosis on IA was calculated per-vessel territory and its incremental value over CTA and CTP defined with Cohen’s Kappa.

Results

Out of 73 patients recruited, 33 were excluded due to contraindications: ACS within 48 hours or unstable angina (n=4), long QT interval (n=6), severe aortic stenosis (n=4), severe left main stenosis (n=2), renal dysfunction (n=10), AV- block II/III (n=2), severe obstructive pulmonary disease (n=2), LV-dysfunction/heart failure (n=4) or refused consent (n=3). One patient agreed to CMR but refused CT. 9 patients were examined with stress CTP only but not with CMR. 39 subjects completed stress CTP. 30 patients were examined with stress CTP and CMR. 25 patients had IA within 6 weeks. The study population is shown in Table 1.

Radiation dose estimates

The 2-step myocardial CTP protocol resulted in an effective radiation dose of 2.5mSv ±2.1 (range, 1.3-6.7), CTDI_{vol} was 10.94mGy±9 (range, 4.8-42.3) and DLP 191mGy/cm±128 (range, 95-698). Scan time for high-pitch stress CTP was 0.31s (range, 0.24-0.37), scan length 14.3cm (range, 10.9-17.4). Effective radiation dose for stress and rest were 0.93mSv±0.18 (range, 0.75-1.48) and 1.59mSv±1.3 (range, 0.53-5.8mSv), respectively. For rest CTP, high-pitch was
applied in 28/39 (72%) patients with a HR<63bpm, and prospective ECG-triggered dual-step-and-shot\textsuperscript{12} in the remaining 11.

**Exams and heart rates**

All patients were in sinus rhythm. Mean HR during stress CTP was 69bpm±11 (range, 51-99). During rest, HR was 58bpm±11 (range, 44-86). In 4 of 30 patients, adenosine was stopped before reaching 3 minutes because of cessation criteria (n=2: at 2 minutes, n=1: at 1:45 min due to angina and in n=1 at 2:50 minutes because of angina/ST-depression). During CMR, adenosine was stopped in 5 patients before reaching 3 minutes due cessation criteria (angina).

In 30 patients who underwent both stress CTP and CMR, among 480 myocardial segments, there were 103 with complete reversible (CR) (Figure 2), 41 with partial reversible (PR) ischemia (Figure 3) and 52 with myocardial infarcts (Figure 4) (43 fixed defects and 9 with myocardial thinning) by CTP.

**Accuracy of adenosine stress-CTP for detection of “all myocardial perfusion defects” (reversible and fixed) versus CMR**

The accuracy of CTP is presented *at Table 2*. For detection of any myocardial perfusion defects during adenosine, stress CTP had a sensitivity of 78%, a specificity of 87%, and NPV of 84% per myocardial segment compared to combined CMR stress perfusion and DE as reference standard. (ROC: AUC, c=0.84). Per coronary vessel, sensitivity was 96%, specificity 88% and NPV 94%. (AUC, c=0.93). The ICC for intra-individual variations among myocardial segments was very low with 0.105 (95%CI:0.06-0.19) and moderate with 0.59 (95%CI:0.13-0.79) for vessels. GEE showed independency for segments (mean p=0.310). For vessels, the hierarchic model was showed significant variance (p=0.002).
Accuracy of adenosine stress CTP for detection of “reversible” myocardial ischemia versus CMR

The diagnostic accuracy of CTP is shown at Table 3. Per myocardial segment, the diagnostic accuracy of CTP for detection of reversible defects (n=144) on CT during adenosine, as compared to adenosine stress perfusion CMR was: sens. 68%, spec. 88%, NPV 85% (AUC, 0.82) and on per-vessel-based analysis: sens 95%, spec. 96%, NPV 96%. (AUC, c=0.93). The ICC for intra-individual variations was very low with 0.085 (95% CI:0.033-0.21) for segments and fair with 0.49 (95% CI: 0.18-1.32) for vessels, respectively. GEE showed independency for segments (mean p=0.390). Hierarchic model showed a significant variance (p=0.04) for vessels.

The confidence scores for perfusion defects during stress CT were mean 1.3±0.3 and those by CMR 2.1±0.9.

Intraobserver agreement for CTP was good with kappa=0.66±0.17 (range, 0.48-0.80) for rest and stress CTP and interobserver agreement was kappa=0.48±0.2 (range, 0.41-63) and 0.61 (range, 0.25-1), respectively. Interobserver agreement for CMR was kappa=0.72±0.19 (range, 0.28-1) for DE and 0.68±0.2 for perfusion.

Accuracy of adenosine stress CTP and CTA for detection of significant stenosis vs. invasive angiography (IA)

Out of 39 patients who underwent CTP, 25 patients had IA within 6 weeks (mean, 26.0 days) (Figure 5). The accuracy of coronary CTA for detection of >70% stenosis (mean, 86.1%) as compared to IA per-vessel and a per-segment is presented at Table 4. 8 segments with stents (Figure 3) were included.
The accuracy of CTP for the detection of stenosis >70% per vessel is shown at Table 5. Out of 75 vessel territories, there were 6 FP and 1 FN by CTP (accuracy 90%, sensitivity 98%, specificity 60%, NPV 90%). 24/25 pts had >70%stenosis (96%) by IA. All were correctly identified.

When adding CTP to CTA (Table 5), the accuracy of CTA increased from 84% to 95%, and those of CTP from 90% to 95%. The number of FP by CTA decreased from 11 to 4. Out of 4 “FP” there were 3 intermediate (50-70%) stenosis on IA causing reversible ischemia. In one FP case on both CTP and CTA, artifacts mimicked a perfusion defect inferolateral, and CX in-stent lumen was not interpretable. For combined CTA and CTP interpretation, kappa increased to 0.81 from 0.33 for CTA and 0.67 for CTP. Table 6 shows the performance of CTP to detect no, reversible and fixed defects compared to CMR, revealing a good sensitivity and correlation.

Discussion

Our data demonstrates a good diagnostic accuracy of adenosine stress myocardial CTP imaging with 128-slice CT in high-pitch mode for the detection of reversible myocardial ischemia, as compared to the reference standard CMR. The accuracy of stress CTP was higher in a per-vessel territory as compared to a per-segment analysis, likely due to misregistration of myocardial segments between CTP and CMR. We also demonstrate that the diagnostic accuracy of CTA is maintained as compared to IA, even using a comprehensive stress CT protocol. Adenosine stress myocardial perfusion imaging with 128-slice CT in high-pitch mode has the potential to overcome current limitations of coronary CTA, in terms of providing simultaneously evaluation of reversible myocardial ischemia and coronary anatomy from the same datasets with low radiation exposure.
In contrast to previous studies\textsuperscript{7,8}, our study has 2 novelties: First, we compared between stress CTP and stress CMR, while other studies compared SPECT\textsuperscript{7,8}. Second, we applied new CT technology, 128-slice dual source CT using high-pitch ECG-synchronization\textsuperscript{10-11} leading to a substantial decrease in radiation exposure to 2.5mSv. High-pitch mode allows for an ultrafast scan time of <0.4 seconds within one end-diastolic phase, while maintaining uniform contrast enhancement throughout the myocardium and avoiding different timing of contrast perfusion of the myocardium.

Our study results are in line with previous studies\textsuperscript{7,8}, reporting a sens. of 93% and spec. of 74% for CT compared to SPECT and invasive angiography (> 50% stenosis), for first generation 64-slice dual source CT in 33 patients\textsuperscript{7}. Our data show a higher specificity of CTP in a per-vessel-basis, which may be attributed to the improved spatial resolution of CMR as compared to SPECT and to the fact that the pharmacokinetics of iodine and gadolinium-containing contrast agents used for CTP and CMR is closer related.

The second novel aspect of our study encompasses the implementation of a new CT technology, 2nd generation 128-slice DSCT\textsuperscript{10-11} using high-pitch spiral image acquisition at a pitch factor of 3.4, which resulted in about 6-fold lower radiation dose as compared to adenosine stress CT MPI imaging using 1st generation 64-slice DSCT (12.7 mSv)\textsuperscript{7}, and resulted in 10-fold lower radiation dose as compared to the dynamic myocardial perfusion “shuttle-mode” with alternating table positions (9.6mSv x 2)\textsuperscript{16}. In contrast to our “one-shot” technique, the “shuttle-mode” provides the advantage of dynamic “real-time” imaging of myocardial perfusion over a time frame of up to 30 seconds\textsuperscript{16} similar to MR, but does not allow for complementary CTA evaluation. Moreover, presently the z-axis coverage is limited to only 7.3 cm\textsuperscript{16}, and imaging is contained to systole.
The total radiation exposure of 2.5 mSv observed in our series for the combined stress and rest CTP/coronary CTA protocol indeed provides a very reasonable approach in practice. 320-detector volume CT enables imaging of the heart within one heart beat at 16 cm z-axis coverage and allows for myocardial perfusion imaging at higher radiation dose and preserved homogenous attenuation of the myocardium as shown by George et.al\(^8\).

The optimal time point of image acquisition was chosen at one time point, as suggested by a myocardial blood flow (MBF) quantification study\(^17\) showing that the difference in upslope between ischemic and remote myocardium remains relatively constant for several seconds during the entire arterial phase\(^17\) after a minimum delay of 12s. Further, the high-pitch mode is a spiral technique hence provides the advantage that misregistration step artifacts, as observed for prospective ECG-triggering, are avoided.

The potential advantage of CTP over CMR is the complementary acquisition of CT angiography datasets\(^10-11\) allowing for both imaging of coronary anatomy and myocardial perfusion. This is of particular interest for 2 different patient groups: Firstly, in patients with intermediate or high-pre-test probability of CAD scheduled to undergo coronary revascularization, knowledge about any and which myocardial segments exhibit reversible ischemia provides prognostic information and can aid surgical planning in terms of defining which territories most likely will benefit from revascularization.

This applies for both planning of percutaneous interventions such as chronic total occlusions (CTO)\(^18\), or of CABG surgery, for which characterization of lesion and distal vessel morphology, can be provided by CTA. Potentially, CTP may solve another limitation of CTA, the detection of in-stent restenosis\(^19\) (\textit{Figure 2}) which has a sens. and spec of 79\% and 81\%\(^19\), because artifacts from stent-struts causing variable (44-48\%) artificial luminal narrowing\(^20\).
Secondly, in patients presenting with “intermediate stenosis” of 50-70% on coronary CTA, an MPI study (CMR, SPECT or ECG-treadmill) is required to determine whether a following invasive angiography is necessary. In these patients, the addition of an adenosine stress CTP exam may provide this information while adding only little time and efforts for the patient and physician. Another recent study\textsuperscript{21} has shown added value of adenosine stress CTP over CTA by increasing the specificity from 71% to 91%; and the PPV from 66% to 86%, respectively, for detection of significant stenosis on invasive angiography.

Our study corroborates this data\textsuperscript{21} by revealing similar results. Using our two-step CTP-protocol, it was possible to obtain diagnostic image quality of coronary arteries during rest CTP allowing for accurate detection of significant coronary artery stenosis (≥70%) without additional contrast or radiation exposure. The moderate PPV of CTA compared to IA is in line with literature\textsuperscript{1} and can be explained by a high prevalence of severely calcified coronary arteries in our study population with high probability of CAD. Overall diagnostic accuracy of CTA for detection of coronary stenosis using a combined CTA and CTP protocol is maintained\textsuperscript{1-3}.

The PPV of stress CTP was 91%, improved compared to CTA with 67% and 84%, per segment and per vessel, respectively. More importantly, the intermodality agreement between CT and IA, as well as the accuracy of combined CTP and CTA readouts improved from 90 to 95%, and the number of false positive findings decreased from 11 to 4, which is line with literature\textsuperscript{21}. For the rest-CT, high-pitch mode was used if HR <63 bpm, because motion artifacts for coronary imaging occur\textsuperscript{22} at higher HR particularly in the right coronary artery. Therefore we applied prospective dual-step-ECG-triggering\textsuperscript{12} for the rest scan if HR was more than 63 bpm, which allows for cardiac function analysis, and could potentially be used for comprehensive evaluation of regional wall motion abnormalities. For stress CT, high-pitch mode was used in all patients. Despite mean heart rate during adenosine injection being too high to permit reliable analysis of
coronary arteries, image quality of the myocardium is less susceptible to motion artifacts than the coronary arteries and CTP could be assessed in all patients.

Interobserver agreement for CTP was moderate which can be attributed to learning curve because the level of experience between the CT observers was variable.

**Study limitations**

We acknowledge a selection bias, because our study population exhibited high prevalence of CAD affecting interpretation of specificity. High disease prevalence is a study limitation, which does not permit calculating the accuracy per-patient. However the number of diseased versus non-diseased vessels and segments for the stress CTP versus CMP myocardial perfusion analysis was well balanced and independent. Further studies on patients with low-to-intermediate likelihood and a higher prevalence of intermediate stenosis are needed.

Second, we did compare CTA and CTP with invasive angiography in a subset of 25 patients, who had a high prevalence of diseased vessels, hence a bias is introduced for the per-vessel based analysis for the specificity, and NPV lacks statistical power.

Further, some patients had totally occluded or collateralized vessels. In those patients, the myocardial perfusion defects may not strictly be aligned with the AHA- segment based coronary artery territory classification. Therefore we highlight the direct comparison of myocardial perfusion defects by CTP with CMR.

A high percentage of patients had to be excluded due to contraindications, such as renal dysfunction or arrhythmia.

Contrast volume for one CT scan was ~70cc, resulting in a total of ~140cc, which is generally well tolerated in patients with normal kidney function but not appropriate in those with dysfunction.
The additional use of CT delayed-enhancement could improve the accuracy of CT for the detection of myocardial infarctions, but was not included.

**Conclusion**

Adenosine stress myocardial CTP imaging with 128-slice high-pitch DSCT allows for accurate detection of myocardial ischemia and coronary stenosis, using CMR and IA as the reference standard. Reversible myocardial ischemia can be detected at a very low radiation dose.

In summary, 128-dual source CT is able to overcome shortcomings of coronary CTA, in terms of providing information about reversible myocardial ischemia and infarcts in addition to coronary stenosis. There may be 2 potential clinical applications: First, in patients with high coronary risk profile, known CAD, or those with a high calcium score (>400 Agatston Units), the stress CTP could be performed first. Second, in patients exhibiting intermediate (50-70%) stenosis on coronary CTA or in those with in-stent restenosis, CTP could be used. The adenosine stress CT scan could be added after CTA and awaiting elimination of the first contrast bolus (20-30 minutes). Further, in patients scheduled for coronary revascularization such CTO-intervention or CABG surgery, information about both coronary lesion characteristics and myocardial segments with reversible ischemia or infarcts is helpful to plan the procedure.
Disclosures

None.

References


Peterson ED, Wolk MJ, Allen JM, Patel MR.

High spatial resolution myocardial perfusion cardiac magnetic resonance for the detection of coronary artery disease. Eur Heart J. 2008;29: 2148-2155.


Table 1. Patient characteristics (39 patients)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (years)</td>
<td>65.6±10 (range, 49-82)</td>
</tr>
<tr>
<td>gender n (%)</td>
<td>females 3 (0.8%)</td>
</tr>
<tr>
<td>Body mass index (BMI) (kg/m²)</td>
<td>27.8±3.6 (19-34)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>78.3±12 (45-100)</td>
</tr>
<tr>
<td>Coronary risk profile</td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>31 (79%)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>25 (64%)</td>
</tr>
<tr>
<td>Positive family history</td>
<td>11 (28%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>32 (82%)</td>
</tr>
<tr>
<td>diabetes</td>
<td>11 (28%)</td>
</tr>
<tr>
<td>previous myocardal infarct</td>
<td>14 (36%)</td>
</tr>
<tr>
<td>or ACS</td>
<td></td>
</tr>
<tr>
<td>stents</td>
<td>4 (1%)</td>
</tr>
</tbody>
</table>

**Abb:** n=count, ACS= acute coronary syndrome,
Table 2. Diagnostic accuracy of adenosine stress CTP for detection of all (reversible and fixed) myocardial perfusion defects versus CMR perfusion and delayed enhancement

<table>
<thead>
<tr>
<th></th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Per-segment (n=480)</strong></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (163/209)</td>
<td>78% 72–83</td>
</tr>
<tr>
<td>Specificity (238/271)</td>
<td>88% 83–91</td>
</tr>
<tr>
<td>PPV (163/196)</td>
<td>83% 77–88</td>
</tr>
<tr>
<td>NPV (238/284)</td>
<td>84% 79–87</td>
</tr>
<tr>
<td>Accuracy (401/480)</td>
<td>84% 80–87</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Per-vessel (n=90)</strong></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (53/55)</td>
<td>96% 88-99</td>
</tr>
<tr>
<td>Specificity (31/35)</td>
<td>88% 74-95</td>
</tr>
<tr>
<td>PPV (53/57)</td>
<td>93% 83-97</td>
</tr>
<tr>
<td>NPV (31/33)</td>
<td>94% 80-98</td>
</tr>
<tr>
<td>Accuracy (84/90)</td>
<td>93% 86-97</td>
</tr>
</tbody>
</table>

**Abb.** CI=confidence interval. * segments with “myocardial thinning” (n=9) were regarded as infarcts. Positive segments per patient: 40.8% (SD 27.3) (range, 0-81.2%).
Table 3. Accuracy of adenosine stress CTP for diagnosis of reversible myocardial ischemia versus stress CMR

<table>
<thead>
<tr>
<th>Per-segment (n=480)</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (105/154)</td>
<td>68% 61-75</td>
</tr>
<tr>
<td>Specificity (287/326)</td>
<td>88% 84-91</td>
</tr>
<tr>
<td>PPV (105/144)</td>
<td>73% 65-79</td>
</tr>
<tr>
<td>NPV (81/89)</td>
<td>85% 81-89</td>
</tr>
<tr>
<td>Accuracy (393/480)</td>
<td>82% 78-85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Per-vessel (n=90)</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (45/47)</td>
<td>96% 86-99</td>
</tr>
<tr>
<td>Specificity (41/43)</td>
<td>95% 85-99</td>
</tr>
<tr>
<td>PPV (45/47)</td>
<td>96% 86-99</td>
</tr>
<tr>
<td>NPV (41/43)</td>
<td>95% 85-99</td>
</tr>
<tr>
<td>Accuracy (86/90)</td>
<td>96% 89-98</td>
</tr>
</tbody>
</table>
Table 4. Accuracy of Coronary CTA for diagnosis of coronary stenosis >70% vs. Invasive angiography (25 patients): per-segment.

<table>
<thead>
<tr>
<th>Per-segment (n=400)</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (77/80)</td>
</tr>
<tr>
<td></td>
<td>Specificity (282/320)</td>
</tr>
<tr>
<td></td>
<td>PPV (77/115)</td>
</tr>
<tr>
<td></td>
<td>NPV (282/285)</td>
</tr>
<tr>
<td>Accuracy (360/400)</td>
<td>90%</td>
</tr>
</tbody>
</table>
Table 5. CTP, CTA and combined CTA/CTP vs invasive angiography (IA) for detection of >70% stenosis. Per-vessel (n=75)

<table>
<thead>
<tr>
<th></th>
<th>CTP</th>
<th></th>
<th>CTA</th>
<th></th>
<th>CTA/CTP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/n</td>
<td>95%CI</td>
<td>n/n</td>
<td>95%CI</td>
<td>n/n</td>
<td>95%CI</td>
</tr>
<tr>
<td>Sens.</td>
<td>59/60 98%</td>
<td>91-99</td>
<td>59/60 98%</td>
<td>91-99</td>
<td>60/60 100%</td>
<td>94-100</td>
</tr>
<tr>
<td>Spec.</td>
<td>9/15 60%*</td>
<td>36-80</td>
<td>4/15 27%*</td>
<td>11-52</td>
<td>11/15 74%*</td>
<td>48-89</td>
</tr>
<tr>
<td>PPV</td>
<td>59/65 91%</td>
<td>81-95</td>
<td>59/70 84%</td>
<td>86-99</td>
<td>60/64 97%</td>
<td>85-97</td>
</tr>
<tr>
<td>NPV</td>
<td>9/10 90%*</td>
<td>60-98</td>
<td>4/5 80%*</td>
<td>38-96</td>
<td>11/11 100%</td>
<td>87-97</td>
</tr>
<tr>
<td>Accuracy</td>
<td>68/75 90%</td>
<td></td>
<td>63/75 84%</td>
<td></td>
<td>72/75 95%</td>
<td></td>
</tr>
<tr>
<td>kappa</td>
<td>0.67 (0.45-0.89)</td>
<td></td>
<td>0.33 (0.14-0.52)</td>
<td></td>
<td>0.81 (0.59-1.04)</td>
<td></td>
</tr>
</tbody>
</table>

*Specificity and NPV are biased

Table 6. Classification “no”, “reversible” and “fixed” defects by CTP: comparison with CMR

<table>
<thead>
<tr>
<th></th>
<th>Detection rate</th>
<th>False positive</th>
<th>kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/n(%)</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>No defect</td>
<td>238/271(87%)</td>
<td>33</td>
<td>0.63</td>
</tr>
<tr>
<td>Reversible defects</td>
<td>105/154(68%)</td>
<td>39</td>
<td>0.57</td>
</tr>
<tr>
<td>Fixed defect</td>
<td>46/55(83.6%)</td>
<td>6</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Abb.: n=counts
Figure Legends

Figure 1. CT scan protocol: Stress CT perfusion using FLASH (pitch factor, 3.4) was performed after 3 minutes of adenosine injection. An iodine contrast agent (CA 1) bolus (arterial phase, bolus triggering) was injected before stress CT. After a delay of 5 minutes, rest CT was performed following a second contrast agent bolus (CA 2) permitting coronary CT angiography. If heart rate was <63 bpm, FLASH (high-pitch) image acquisition was applied and in heart rates >63 bpm, a SEQUENCE (prospective ECG-triggered) to ensure diagnostic image quality of coronary arteries.

Figure 2. Complete reversible myocardial ischemia. 82 YOM, denovo AP CCS II-III. IA showed multiple 60-70% stenosis in the RCA on IA causing a reversible inferior and infero-septal myocardial perfusion defect on CT (A, B) and CMR (C, D). CX was subtotally 99% occluded matching with a reversible defect infero-lateral on both CT (A, B) and CMR (C, D). Excellent image quality for both CTP and CMR yielding highest confidence. Severely calcified RCA and CX (E) on CTA did not allow for exact evaluation of coronary stenosis.

Figure 3. Partial reversible myocardial ischemia. 69-YOM, asymptomatic, after PTCA and NSTEMI 6 months ago scheduled for invasive angiography. Partial reversible myocardial ischemia anteroseptal (A, stress CT, black arrows and B) and anterior during rest (B, black arrow), correlating with a subendocardial scar at CMR-DE (Panel C, black arrow) with less than 50% transmurality. LAD in-restenosis at proximal stent edge (Panel DE, and F, invasive angiogram). Reversible defect inferior by CTP, caused by RCA stenosis.

Figure 4. 59-YOM with myocardial infarct. CT showed a fixed defect inferoseptal and inferolateral during stress (A) and rest (B) matching with a fixed defect on stress MR (C) and rest MR (D) and delayed enhancement (G) inferoseptal, inferior, and inferolateral. CTA showed RCA occlusion (F) and CX-PL-branch occlusion (G) confirmed by IA (H) and (I), respectively. Beam hardening artifact inferior (A).

Figure 5. Reversible myocardial ischemia. 70-YOF, angina CCS III. Reversible myocardial perfusion defect anterior, septal, inferior and lateral (arrows, A-D) during stress CTP (A,B) and rest CTP (C,D). Lower HU units indicate hypoperfused myocardium (right-sided). LAD occlusion and high-grade CX stenosis by CTA (E) and invasive angiography (IA) (F). RCA occlusion distally (arrow) by CT and IA (G and H). False positive proximal stenosis by CTA (G) being not significant on IA (H). During rest (C,D) streak-like beam hardening artefact inferior.
Adenosine Stress High-pitch 128-slice Dual Source Myocardial Computed Tomography Perfusion For Imaging Of Reversible Myocardial Ischemia: Comparison with Magnetic Resonance Imaging

Gudrun Feuchtner, Robert Goetti, André Plass, Monika Wieser, Hans Scheffel, Christophe Wyss, Paul Stolzmann, Olivio Donati, Johannes Schnabl, Volkmar Falk, Hatem Alkadhi, Sebastian Leschka and Ricardo C. Cury

_Circ Cardiovasc Imaging_. published online August 23, 2011;
_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/early/2011/08/23/CIRCIMAGING.110.961250

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Imaging_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Imaging_ is online at:
http://circimaging.ahajournals.org//subscriptions/