Diagnostic accuracy of computed tomography coronary angiography and evaluation of stress-only single-photon emission computed tomography/computed tomography hybrid imaging: comparison of prospective electrocardiogram-triggering vs. retrospective gating

Husmann, L; Herzog, B A; Gaemperli, O; Tatsugami, F; Burkhard, N; Valenta, I; Veit-Haibach, P; Wyss, M T; Landmesser, U; Kaufmann, P A


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Abstract

Aims To determine diagnostic accuracy, effective radiation dose, and potential value of computed tomography coronary angiography (CTCA) for hybrid imaging with single-photon emission computed tomography (SPECT) comparing prospective electrocardiogram (ECG)-triggering vs. retrospective ECG-gating. Methods and results Two hundred patients underwent standard myocardial stress/rest-SPECT perfusion imaging, which served as standard of reference. One hundred consecutive patients underwent 64-slice CTCA using prospective ECG-gating, and were compared with 100 patients who had previously undergone CTCA using retrospective ECG-gating. For predicting ischaemia, CTCA with prospective ECG-triggering and a stenosis cut-off >50% had a per-vessel sensitivity, specificity, negative, and positive predictive value of 100, 84, 100, and 30%; respective values for CTCA with retrospective ECG-gating were similar (P = n.s.): 86, 83, 98, and 33%. Combining CTCA with stress-only SPECT revealed 100% clinical agreement with regard to perfusion defects, and provided additional information in half the patients on preclinical coronary findings. Effective radiation dose was 2.2 +/- 0.7 mSv for CTCA with prospective ECG-triggering, and 19.7 +/- 4.2 mSv with retrospective ECG-gating (P < 0.001) (5.4 +/- 0.8 vs. 24.1 +/- 4.3 mSv for hybrid imaging). Conclusion Prospective ECG-triggering for CTCA reduces radiation dose by almost 90% without affecting diagnostic performance. Combined imaging with stress-only SPECT is an attractive alternative to standard stress/rest-SPECT for evaluation of coronary artery disease, offering additional information on preclinical atherosclerosis.
Title: Diagnostic Accuracy of CT Coronary Angiography and Evaluation of Stress-only SPECT/CT Hybrid Imaging: Comparison of Prospective ECG-triggering versus Retrospective Gating

Article Type: Clinical paper

Keywords: low dose CT; prospective ECG-triggering; retrospective ECG-gating; computed tomography coronary angiography; diagnostic accuracy; hybrid imaging; stress-only SPECT

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Suggested Reviewers:

Opposed Reviewers:
Professor Frans Van de Werf
Editor-in-Chief
The European Heart Journal

Zurich, August 8th 2008

Manuscript:
“Diagnostic accuracy of CT coronary angiography and evaluation of stress-only SPECT/CT hybrid imaging: comparison of prospective ECG-triggering versus retrospective gating”

Former title:
“Low Dose Hybrid Cardiac Imaging with Myocardial Perfusion Stress SPECT and prospectively gated CT Coronary Angiography”

Dear Prof. Van de Werf

Thank you for your letter regarding the above manuscript offering us the opportunity to resubmit a revised version to European Heart Journal.

We have thoroughly revised the manuscript according to the reviewers’ comments. Specifically, we have explained in detail how we have calculated effective radiation dose for the CT as well as the SPECT protocols. We have, however, not excluded patients with known CAD although the reviewer had originally requested this. The reason for not excluding them is that in this validation study we prospectively included consecutive patients for the hybrid protocol and did not exclude patients with known CAD in order to ensure true positive findings allowing to calculate a specificity and positive predictive value. In fact, an agreement between hybrid SPECT/CT and
standard stress/rest SPECT would be less meaningful if only negative findings would be included.

In addition, we have – according to the editorial office advice - now included the key information of the manuscript with the validation of the two different CT protocols (prospective triggering versus retrospective gating). Thus, the revised manuscript includes now two parts: The first part deals with the accuracy of prospective (low dose) CTCA to predict hemodynamic relevant lesions and compares this to conventional retrospective CTCA. In the second part we validated a new algorithm for evaluation of unknown CAD by hybrid imaging combining CTCA with low dose stress only perfusion SPECT. For both parts standard stress/rest SPECT MPI served as standard of reference.

In brief, our study shows that prospective ECG-triggering for CTCA reduces radiation dose by almost 90% without affecting diagnostic performance. Second, combined imaging of low dose CTCA with stress-only SPECT is an attractive alternative to standard stress/rest SPECT for evaluating CAD.

We hope that you will feel able to accept the revised manuscript in its present form and we are looking forward to your kind answer.

Sincerely yours,

Philipp Kaufmann, MD
Head Nuclear Cardiology
Response to Reviewers' Comments:

**Reviewer #1:**
1. **Target population**
As mentioned in the paper, the target population should be patients with low-intermediate pre-test likelihood for CAD. However, the authors included also 16 patients with known CAD, where this technique does not really give additional information. In my opinion these patients should not be included in the final version of the paper. Also it is now clear how many patients were exactly included: 76 patients or 51 patients (page 8)?

**Authors:**
We agree that the strengths of CTCA is the high negative predictive value, making this tool most suitable for evaluation of CAD in a low to intermediate likelihood population for CAD. This also holds true for the hybrid protocol. However, in this validation study we prospectively included consecutive patients for the hybrid protocol and did not exclude patients with known CAD in order to ensure true positive findings allowing to calculate a specificity. In fact, an agreement between hybrid SPECT/CT and standard stress/rest SPECT would be less meaningful if only negative findings would be included. This has been clarified in the discussion section of the revised manuscript.

2. **Methods: radiation dose**
It is not clear to me how radiation dose was calculated. Was it estimated or calculated and how was this done? The text is very brief and unclear on this.

**Authors:**
We have given more details on this key topic of the present manuscript. The new paragraph on effective radiation dose now reads:

“The total effective dose of CTCA was calculated as the product of the dose-length product (DLP) times a conversion coefficient for the chest (k = 0.017 mSv/mGy x cm) (ref. 5). For SPECT the effective radiation dose was estimated as previously suggested (6.7 mSv/GBq) (ref. 5) plus the dose for CT attenuation correction (DLP X k).”

3. **Methods: image evaluation**
The authors show some nice examples of fused images. Were these images used for analysis of the data or were the analyzed separately? Could this have introduced some bias?

**Authors:**
We have not used the hybrid images for analysis as this would have introduced a bias by unblinding the data. After analysis, some images were fused for presentation purposes only, as this could be used for analysis in a clinical setting without blinding.

4. **Clinical implications**
The proposed algorithm makes sense in patients without known CAD. What do the authors propose as "next step" if a perfusion defect is seen on the stress images, with a stenosis on CT? Perform a rest study, go straight to the cathlab or something else? The authors should also mention that this technique is only suitable for younger patients (without too much calcifications) without significant comorbidities (especially renal dysfunction)

**Authors:**
We agree, as motioned above, that the proposed hybrid protocol seems to prove most useful in patients without know CAD. In our study we did not determine a pathologic hybrid finding should be completed by a resting SPECT scan or directly by invasive coronary angiography. Therefore we were reluctant to provide a firm statement on this. However, we felt that this decision would probably best be based on the whole clinical context. We have elaborated on this in the discussion section of the revised manuscript.
Diagnostic Accuracy of CT Coronary Angiography and Evaluation of Stress-only SPECT/CT Hybrid Imaging: Comparison of Prospective ECG-triggering versus Retrospective Gating

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Abstract

Aims: To determine diagnostic accuracy, effective radiation dose, and potential value of computed tomography coronary angiography (CTCA) for hybrid imaging with single-photon emission computed tomography (SPECT) comparing prospective electrocardiogram (ECG)-triggering versus retrospective ECG-gating.

Methods and results: Two hundred patients underwent myocardial SPECT perfusion imaging, which served as standard of reference. One hundred consecutive patients underwent 64-slice CTCA using prospective ECG-gating, and were compared to 100 patients who had previously undergone CTCA using retrospective ECG-gating. For predicting ischemia CTCA with prospective ECG-triggering and a stenosis cut-off >50% had a per-vessel sensitivity, specificity, positive and negative predictive value of 100%, 84%, 100%, and 30%, respective values for CTCA with retrospective ECG-gating were similar (P=n.s.): 86%, 83%, 98%, and 33%. Combining CTCA with stress-only-SPECT revealed 100% clinical agreement with regard to perfusion defects, and provided additional information in half the patients on preclinical coronary findings. Effective radiation dose was 2.2±0.7mSv for CTCA with prospective ECG-triggering, and 19.7±4.2mSv with retrospective ECG-gating (P<0.001) (5.4±0.8 vs. 24.1±4.3mSv for hybrid imaging).

Conclusion: Prospective ECG-triggering for CTCA reduces radiation dose by almost 90% without affecting diagnostic performance. Combined imaging with stress-only-SPECT is an attractive alternative to standard stress/rest-SPECT for evaluation of coronary artery disease, offering additional information on premature atherosclerosis.
Keywords: low dose CT, prospective ECG-triggering, retrospective ECG-gating, computed tomography coronary angiography, diagnostic accuracy, hybrid imaging, stress-only SPECT
Introduction

In the past years computed tomography coronary angiography (CTCA) has been used increasingly in the assessment of coronary artery disease (CAD), as it offers high diagnostic accuracy in stenosis detection,\textsuperscript{1-4} short examination time, minimal side effects a part from the potential harm of radiation-induced neoplasms, which has evoked a vivid controversy on the clinical benefit of CTCA. This has induced the search for strategies to minimize the radiation dose while maintaining image quality. Several technical advances have allowed to decrease the dose from originally 20-25 mSv\textsuperscript{4} to 10-15 mSv by use of electrocardiogram (ECG)-gated tube modulation\textsuperscript{5} and even below 10 mSv by further optimizing scanning parameters of CTCA with retrospective ECG-gating.\textsuperscript{6} A recent milestone for wide clinical acceptance of CTCA was the introduction of prospective ECG-triggering, by which scanning is limited to a narrow predefined enddiastolic phase resulting in a massive reduction of radiation exposure to a range of 1-3 mSv.\textsuperscript{7} The validity of this new low dose protocol has been confirmed in a larger unselected patient population\textsuperscript{8} and preliminary reports encourage the use of this protocol in latest generation CT scanners with 320 slices.\textsuperscript{9} However, at present no data exist on the performance of CTCA with retrospective ECG-gating vs. CTCA with prospective ECG-triggering in comparison to a standard of reference.

As objective proof of ischemia is the main determinant for clinical decision making in chronic stable CAD\textsuperscript{10-12} we have used myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) as standard of reference. However, as CTCA visualizes coronary artery stenoses directly, and MPI identifies ischemia, both methods may also provide complementary information on CAD,\textsuperscript{13} and hybrid examinations may facilitate a comprehensive interpretation of coronary lesions and their pathophysiologic relevance.\textsuperscript{13-16} Effective radiation doses
for hybrid imaging with SPECT MPI and CTCA using retrospective ECG-gating of up to 41 mSv\textsuperscript{17} have been reported in the literature, precluding its widespread clinical use, while prospective ECG-triggering may overcome this drawback. A further decrease in radiation dose of hybrid imaging could be achieved by confining the SPECT scan to stress-only, as recently suggested for low pretest probability populations.\textsuperscript{18}

Therefore, the purpose of the present study was twofold: First, to compare the diagnostic accuracy of CTCA with low-dose prospective ECG-triggering versus standard retrospective gating for detecting hemodynamic relevant coronary lesions; and second, to validate a new algorithm for evaluation of unknown CAD by hybrid imaging combining CTCA with low-dose stress-only SPECT.
Methods

Study design

Each patient underwent low-dose stress/high-dose rest-SPECT and CTCA for clinical indication.

First step: Findings from both CTCA acquisition protocols were separately analyzed and compared to SPECT results.

Second step: Two independent blinded readers analyzed either the paired stress-SPECT plus CTCA (CTCA/stress-SPECT) or the stress-SPECT plus the rest-SPECT scan (stress/rest-SPECT).

Clinical study end points were, first the direct comparison of total effective radiation dose and diagnostic accuracy of both CTCA protocols, and, second the comparison of hybrid CTCA/stress-SPECT versus standard stress/rest-SPECT with regard to: agreement on presence or absence of ischemic coronary heart disease, information on premature CAD, total effective radiation dose and total examination duration.

Patient groups

One-hundred consecutive patients with suspected (n=85) or known (n=15) CAD referred for MPI with SPECT and CTCA using prospective ECG-triggering were prospectively enrolled in the present study if none of the following exclusion criteria were present: hypersensitivity to iodinated contrast agent, renal insufficiency (creatinine levels >150 µmol/L, or >1.7mg/dl), non-sinus rhythm, or previous coronary bypass surgery. These patients were compared with 100 retrospectively enrolled patients, who had previously undergone MPI and CTCA using retrospective ECG-
gating, matched for the presence of known CAD, heart rate, and body mass index (BMI).

The study protocol was approved by the institutional review board and written informed consent was obtained.

**CTCA data acquisition and post-processing**

All 200 patients received a single dose of 2.5 mg isosorbiddinitrate sublingual (Isoket, Schwarz Pharma, Monheim, Germany) 2 min prior to the scan. In addition, intravenous metoprolol (5 to 20 mg) (Beloc, AstraZeneca, London, UK) was administered prior to the CTCA examination if necessary to achieve a target heart rate <65 bpm. For CTCA, 80 ml of iodixanol (Visipaque 320, 320 mg/mL, GE Healthcare, Buckinghamshire, UK) at a flow rate of 5 mL/s followed by 50 ml saline solution was injected into an antecubital vein via an 18-gauge catheter. Bolus tracking was performed with a region of interest placed into the ascending aorta.

All CTCA examinations were performed on a LightSpeed VCT XT scanner (GE Healthcare) using two different scanning protocols:

*Prospective ECG-triggering:* slice acquisition 64 × 0.625 mm, smallest x-ray window (only 75% of the R-R-interval; padding set to 0 ms), z-coverage 40 mm with an increment of 35 mm, gantry rotation time 350 ms, body mass index (BMI)-adapted tube voltage (100 - 120kV) and effective tube-current (450 - 700mA).

*Retrospective ECG-gating:* slice acquisition 64 × 0.625 mm, z-coverage 40 mm, heart rate adapted pitch ranging between 0.18 and 0.26, gantry rotation time 350 ms, tube voltage 120 kV, BMI-adapted effective tube-current (280 - 750mA), and ECG-adapted tube modulation (i.e. reduction to about 40% of nominal tube current during systole to mid-diastole). CT data sets were retrospectively reconstructed in
mid-to end-diastolic phases and additional phases if needed for optimal coronary artery visualization.

CTCA image quality was assessed in all coronary segments\textsuperscript{19} of all patients using a previously reported scoring system.\textsuperscript{20} If one or more segments in a patient were rated “non-diagnostic”, then the examination was excluded from further analysis (for retrospective ECG-gating an examination was excluded from further analysis, if at least one coronary segment was considered “non-diagnostic” in all reconstructed phases of the R-R interval).

\textbf{SPECT data acquisition and post-processing}

SPECT data acquisition was performed on a dual-head detector camera (Ventri, GE Healthcare, Milwaukee, WI, USA), and all patients underwent a 1-day stress (0.14 mg/kg/min adenosine i.v.) /rest MPI protocol using a dose of approximately 300 MBq and 900 MBq of 99mTc tetrofosmin, respectively. Emission data were acquired with a parallel-hole, low-energy, high-resolution collimator with a 20\% symmetric window centered at 140 keV. Further acquisition parameters were 3° rotation per stop, 180° each head, and 25 s per projection. Acquisitions were gated for 16 frames per R-R cycle with an acceptance window of 50\%. All patients underwent low-dose, unenhanced CT for attenuation correction on a LightSpeed VCT XT scanner (GE Healthcare), as previously reported in detail.\textsuperscript{21}

\textbf{Diagnostic accuracy}

CTCA images were evaluated and classified by two independent readers, blinded to the results of SPECT, using axial source images, multi-planar reformations, and thin-slab maximum intensity projections. Coronary arteries were
visually assessed for the presence of narrowing of the coronary luminal diameter >50% and >75%.

SPECT data was analyzed, blinded to the results of CTCA, with regard to the presence of reversible and/or fixed perfusion defects on short-axis, horizontal and vertical long-axis slices as well as on the polar maps. Left ventricular perfusion defects were attributed to three vascular territories: left anterior descending artery (LAD) included the apical, anterior, septal wall, circumflex artery (CX) included the lateral wall, and right coronary artery (RCA) included the inferior wall.

**Effective radiation dose**

The total effective dose of CTCA was calculated as the product of the dose-length product (DLP) times a conversion coefficient for the chest (k = 0.017 mSv/mGy x cm).\(^5\) For SPECT the effective radiation dose was estimated as previously suggested (6.7mSv/GBq)\(^5\) plus the dose for CT attenuation correction (DLP x conversion coefficient for the chest).

**Duration of examination protocols**

The routine time schedule for the standard stress/rest-SPECT protocol\(^22\) used at our institute requires a period of 90 min between each injection of \(^{99m}\)Tc-Tetrofosmin and the following data acquisition. CTCA is routinely performed between the application of the tracer at stress and the first SPECT data acquisition. For all patients the total time for both protocols was assessed.

**Statistical analysis**

Quantitative variables were expressed as mean ± standard deviation and categorical variables as frequencies, or percentages. Sensitivity, specificity, positive
predictive value (PPV), and negative predictive value (NPV) were calculated, Stress/rest MPI with SPECT was considered the standard of reference. Because of the interdependencies between different vessels, the statistics were also calculated on a per-patient basis (presence of at least one significant coronary artery stenosis or absence of any significant stenosis in each patient). We took into account the clustered nature of the data (i.e. the fact that there were not 600 independent vessels but instead clusters of vessels in 200 patients). For these analyses a proportion-procedure for survey data of the Stata software (Stata 10.0, StataCorp, College Station, Texas) with the patient as primary sample unit was performed to address dependencies between the vessels. Differences between the two matched patient populations regarding diagnostic performance were tested for significance by using $\chi^2$-tests for comparison of cross tables. For further comparison, Mann-Whitney-U-tests were performed for: total effective radiation dose, heart rate, BMI, age. $\chi^2$-tests were used to determine differences in gender, coronary risk factors, clinical symptoms, and prevalence of known CAD. Differences between CTCA/stress-SPECT and standard stress/rest-SPECT in total radiation dose and total time between both protocols were determined using a paired Student’s t-test. A P-value of <0.05 was considered to indicate statistical significance. SPSS software (SPSS 15.0, Chicago, ILL, USA) was used for statistical testing.
Results

Fifteen patients in the group scanned with prospective ECG-triggering had to be excluded because of nondiagnostic CTCA image quality in at least one coronary segment, due to breathing artifacts (n=5), or motion artifacts (n=10). Similarly, 13 patients with retrospective ECG-gated CTCA were excluded because of breathing artifacts (n=6), occurrence of a premature ventricular beat during scanning (n=1), or coronary motion artifacts (n=6). Demographics of the final two patient populations are given in table 1.

Diagnostic accuracy

Prospective ECG-triggering: CTCA revealed 58 coronary vessels (28%) with stenoses >50% in 29 of 85 patients (34%), and 18 vessels (7%) with stenoses >75% in 12 patients (14%). In this group, MPI with SPECT detected perfusion defects in 20 vascular territories (8%) of 18 patients (21%); while 5 of the defects were fixed (scar) 11 were reversible (ischemia), and 2 were partly fixed and partly reversible (mixed defects).

Retrospective ECG-gating: 62 coronary vessels (24%) with stenoses >50% in 38 of 87 patients (44%), and 24 vessels (9%) with stenoses >75% in 17 patients (20%) were observed on CTCA scans. Perfusion defects in 27 (10%) vascular territories of 23 patients (26%) were detected by MPI with SPECT, i.e. 8 fixed, 15 reversible, and 4 mixed defects.

The diagnostic performance of CTCA by prospective ECG-triggering was comparable to retrospective ECG-gating (table 2). Regardless of the scanning technique, CTCA is more sensitive and offers a higher NPV for a stenosis cut-off >50% compared to >75%. Conversely, sensitivity and NPV decrease, while specificity and the PPV increase when a cut-off >75% is chosen.
Hybrid imaging

*CTCA/stress-SPECT with prospective ECG-triggering* identified the same 18 patients to have abnormal perfusion, as the standard stress/rest-SPECT protocol, resulting in a clinical agreement of 100% (*Figure 1*). CTCA provided additional information in 38/85 patients (45%), i.e. intermediate coronary lesions (n=22), nonstenosing coronary plaque (n=15), and coronary anomaly (n=1) (*Figure 2*).

*CTCA/stress-SPECT with retrospective ECG-gating* identified the same 18 patients to have abnormal perfusion, as the standard stress/rest-SPECT protocol, also resulting in a clinical agreement of 100%. CTCA provided additional information in 43/87 patients (49%), i.e. intermediate coronary lesions (n=20), nonstenosing coronary plaque (n=22), and coronary anomaly (n=1).

The time schedule of the CTCA/stress-SPECT examination protocol was shorter as compared to standard stress/rest SPECT (130 vs. 245 min, \( P < 0.001 \)), as all CTCA examinations (either with prospective ECG-triggering or with retrospective ECG-gating) were performed in the 90 min between the first injection of \(^{99m}\text{Tc-Tetrofosmin}\) and stress data acquisition.

Total effective radiation dose

The mean total effective radiation dose of CTCA with prospective ECG-triggering was 2.2±0.7 mSv (range: 1.0-3.3 mSv), representing a reduction of about 90% as compared to the 19.7±4.2 mSv (range: 11.5-33.0 mSv) obtained with retrospective ECG-gating (\( P < 0.001 \)).

Radiation exposure from SPECT was – by definition of the study design – comparable in both groups: i.e. 9.6±0.7 mSv (range: 8.2-12.5 mSv) in the
prospectively triggered group, and 10.7±1.1 mSv (range: 8.5-14.4 mSv) in the group with retrospective ECG-gating.

Combing stress-only-SPECT with prospective ECG-triggering allows a significant reduction of total effective radiation dose, as compared to hybrid imaging with retrospective ECG-gating (5.4±0.8 vs. 24.1±4.3 mSv, \( P<0.001 \)).
Discussion

The main findings of the present study are twofold: First, it documents that prospective ECG-triggering provides an excellent diagnostic accuracy, comparable to retrospective ECG-gating, despite a decrease in radiation dose by about 90%. Second, we have validated a new low-dose hybrid SPECT/CTCA algorithm for assessment of CAD allowing reduction in protocol time as well as in radiation dose at maintained accuracy compared to stress/rest SPECT offering additional clinical information.

Conventional spiral CTCA protocols using retrospective ECG-gating have been shown to be associated with high total radiation doses between 9.4 and 21.4 mSv.\textsuperscript{4,23} With the introduction of prospective ECG-gating, however, the total radiation dose of CTCA could be reduced down to 2.1 mSv.\textsuperscript{7} Only one study\textsuperscript{24} has directly compared total effective radiation doses of the two protocols in a head-to-head comparison, describing a 79% decrease from CTCA with retrospective ECG-gating (20.0 mSv) to CTCA with prospective ECG-triggering (4.1 mSv), which is very similar to the results in the two matched patient populations of the present study (i.e. 2.2 and 19.7 mSv).

Our study provides evidence that accuracy of CTCA is preserved even after introducing the prospective ECG-triggering protocol. No data exists on direct comparison between the two protocols with regard to diagnostic performance, although preliminary data have proven the feasibility and documented preserved image quality with the new dose saving protocol.\textsuperscript{7,8,24,25} The present data not only confirm the substantial reduction in effective radiation dose but also document that the accuracy of CTCA with prospective ECG-triggering equals the accuracy of
retrospectively gated CTCA. As the reduction in radiation dose is striking, the widespread use of prospective ECG-gating may now be envisaged. Our results display an excellent NPV but modest a PPV in the detection of ischemic heart disease, especially when a cut-off for luminal narrowing is chosen at 50%. This is in line with previous results,\textsuperscript{26-28} and concurs with the generally accepted fact that the strengths of CTCA lies in its excellent ability to rule out CAD. As a consequence most recommendations consider the use of CTCA mainly in low to intermediate risk populations,\textsuperscript{29} in which event rate and mortality are low and unlikely to be further lowered by any diagnostic or therapeutic procedure. Therefore the bars are very high for any diagnostic tool to keep a positive balance between harms and benefits. This is reflected by the ongoing controversy on the potential carcinogenic risk of the effective radiation dose and its justification for a purely diagnostic application. In this context prospective ECG-triggering represents a milestone as it allows accurate CAD assessment with low-dose CTCA, which appears to be an ideal “gate-keeper” for the assessment of unknown CAD in selected patient populations (i.e. low to intermediate pre-test probability) due to its high NPV, and may offer an alternative to SPECT. CTCA is less expensive and the examination time is shorter as compared to MPI with SPECT, although new multi-headed SPECT systems may allow considerable shortening of scan duration.

In clinical routine standard stress/rest SPECT MPI scans are important to determine the reversibility of perfusion defects in patients with a history of myocardial infarction.\textsuperscript{22} By contrast, in a patient population with low to intermediate pretest probability and unknown CAD the aim of any test is to reveal the presence of CAD, while potential discrimination of scar from ischemia remains beyond the primary focus of the examination. In patients with normal myocardial perfusion at stress
however, subclinical, yet prognostically relevant \(^{30}\) CAD may be present and patients may benefit from risk factor modification or even specific treatment for CAD.\(^{31}\) The present study demonstrates that low dose CTCA/stress-SPECT offers such additional information on premature CAD in a large proportion of patients at no cost of additional radiation exposure. Furthermore, hybrid cardiac imaging offers a high confidence in image interpretation as the occurrence of equivocal findings in one modality may be supplemented by the other.\(^{32}\) This seems to be particularly important when CTCA is acquired with the prospective ECG-gating, as the performance of this new technique may be prone to artifacts, especially at higher heart rates.\(^{7}\)

We acknowledge the following limitations to our study. After the matching of two patient cohorts, several patients had to be excluded from further analysis because of non-diagnostic image quality in CTCA. This however, applies to both study groups, which therefore remained well matched with regard to heart rate and BMI or presence of known CAD. Furthermore, we have included patients with known CAD, although our CTCA/stress-SPECT algorithm appears most suitable for the assessment of patients with unknown CAD, and does not allow distinguishing reversible (ischemia) from fixed defects (scar). Nevertheless, these patients were included for validation purposes to ascertain true positive findings and allow meaningful analysis. We did not determine whether a pathologic CTCA/stress-SPECT finding should be completed by a rest-scan or directly by invasive coronary angiography, as this decision would probably best be driven by clinical context.

The use of prospective ECG-triggering for CTCA allows reduction of radiation dose by almost 90% without affecting diagnostic performance. Hybrid imaging
combining CTCA with stress-only-SPECT is an attractive alternative to standard stress/rest SPECT for the detection of CAD, offering additional information on premature atherosclerosis.
Funding

The study was supported by a grant from the Swiss National Science Foundation (SNSF-professorship grant No. PP00A-114706) and by the ZIHP (Zurich Center for Integrative Human Physiology, University of Zurich, Switzerland).
Conflict of interest

None.
References


Cardiology and Cardiac CT of the European Society of Cardiology and the European Council of Nuclear Cardiology. *Eur Heart J* 2008; **29**:531-556.


Figure legends

Figure 1:

Fused stress 99Tc-tetrofosmin perfusion SPECT/CTCA image (radiation dose from CTCA 2.2 mSv, from stress-SPECT 2.5 mSv), showing a lateral perfusion defect (arrows heads), served by the stented CX. Sequential intermediate lesions in the LAD (arrows) are not hemodynamically relevant (no perfusion defect).

Figure 2:

Fused stress 99Tc-tetrofosmin perfusion SPECT/CTCA image (radiation dose from CTCA 1.3 mSv, from stress-SPECT 2.2 mSv) reveals normal myocardial perfusion, but non-significant vessel wall irregularities in the proximal LAD (arrows heads), as well as a coronary anomaly (arrow; origin of the RCA from the left coronary sinus).
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<td>Diabetes</td>
<td>11</td>
<td>11</td>
<td>0.95</td>
</tr>
<tr>
<td>Positive family history</td>
<td>22</td>
<td>29</td>
<td>0.21</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>41</td>
<td>43</td>
<td>0.65</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>35</td>
<td>21</td>
<td>0.03*</td>
</tr>
<tr>
<td>Typical angina</td>
<td>23</td>
<td>16</td>
<td>0.23</td>
</tr>
<tr>
<td>Atypical chest pain</td>
<td>22</td>
<td>38</td>
<td>0.003*</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>11</td>
<td>10</td>
<td>0.86</td>
</tr>
</tbody>
</table>

* indicates statistical significance
Table 2. Diagnostic accuracy of CTCA

<table>
<thead>
<tr>
<th></th>
<th>Retrospective ECG-gating</th>
<th>Prospective ECG-triggering</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any perfusion defect</td>
<td>Any perfusion defect</td>
</tr>
<tr>
<td></td>
<td>&gt;50% (%)</td>
<td>&gt;50% (P =)*</td>
</tr>
<tr>
<td></td>
<td>&gt;75% (%)</td>
<td>&gt;75% (P =)*</td>
</tr>
<tr>
<td></td>
<td>Reversible defects only</td>
<td>Reversible defects only</td>
</tr>
<tr>
<td></td>
<td>&gt;50% (%)</td>
<td>&gt;50% (P =)*</td>
</tr>
<tr>
<td></td>
<td>&gt;75% (%)</td>
<td>&gt;75% (P =)*</td>
</tr>
<tr>
<td>patient-based:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>91 (0.74)</td>
<td>94 (0.74)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>73 (0.61)</td>
<td>77 (0.61)</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>96 (0.52)</td>
<td>98 (0.52)</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>55 (0.76)</td>
<td>52 (0.76)</td>
</tr>
<tr>
<td>vessel-based:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>85 (0.99)</td>
<td>85 (0.99)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>83 (0.75)</td>
<td>83 (0.75)</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>98 (0.71)</td>
<td>99 (0.71)</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>37 (0.33)</td>
<td>29 (0.33)</td>
</tr>
</tbody>
</table>

* Comparison versus retrospective ECG-gating
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Abstract

Aims: To determine diagnostic accuracy, effective radiation dose, and potential value of computed tomography coronary angiography (CTCA) for hybrid imaging with single-photon emission computed tomography (SPECT) comparing prospective electrocardiogram (ECG)-triggering versus retrospective ECG-gating.

Methods and results: Two hundred patients underwent myocardial SPECT perfusion imaging, which served as standard of reference. One hundred consecutive patients underwent 64-slice CTCA using prospective ECG-gating, and were compared to 100 patients who had previously undergone CTCA using retrospective ECG-gating.

For predicting ischemia CTCA with prospective ECG-triggering and a stenosis cut-off >50% had a per-vessel sensitivity, specificity, positive and negative predictive value of 100%, 84%, 100%, and 30%, respective values for CTCA with retrospective ECG-gating were similar (P=n.s.): 86%, 83%, 98%, and 33%. Combining CTCA with stress-only-SPECT revealed 100% clinical agreement with regard to perfusion defects, and provided additional information in half the patients on preclinical coronary findings. Effective radiation dose was 2.2±0.7mSv for CTCA with prospective ECG-triggering, and 19.7±4.2mSv with retrospective ECG-gating (P<0.001) (5.4±0.8 vs. 24.1±4.3mSv for hybrid imaging).

Conclusion: Prospective ECG-triggering for CTCA reduces radiation dose by almost 90% without affecting diagnostic performance. Combined imaging with stress-only-SPECT is an attractive alternative to standard stress/rest-SPECT for evaluation of coronary artery disease, offering additional information on premature atherosclerosis.