Early Resting Myocardial Computed Tomography Perfusion for the Detection of Acute Coronary Syndrome in Patients With Coronary Artery Disease

Amit Pursnani, MD; Ashley M. Lee, MD; Thomas Mayrhofer, PhD; Waleed Ahmed, MD; Shanmugam Uthamalingam, MD; Maros Ferencik, MD, PhD; Stefan B. Puchner, MD; Fabian Bamberg, MD, MPH; Christopher L. Schlett, MD, MPH; James Udelson, MD; Udo Hoffmann, MD, MPH; Brian B. Ghoshhajra, MD, MBA

Background—Acute rest single-photon emission computed tomography-myocardial perfusion imaging (SPECT-MPI) has high predictive value for acute coronary syndrome (ACS) in emergency department patients. Prior studies have shown excellent agreement between rest/stress computed tomography perfusion (CTP) and SPECT-MPI, but the value of resting CTP (rCTP) in acute chest pain triage remains unclear. We sought to determine the diagnostic accuracy of early rCTP, incremental value beyond obstructive coronary artery disease (CAD; ≥50% stenosis), and compared early rCTP to late stress SPECT-MPI in patients with CAD presenting with suspicion of ACS to the emergency department.

Methods and Results—In this prespecified subanalysis of 183 patients (58.1±10.2 years; 33% women), we included patients with any CAD by coronary computed tomography angiography (CCTA) from Rule Out Myocardial Infarction Using Computer-Assisted Tomography I. rCTP was assessed semiquantitatively, blinded to CAD interpretation. Overall, 31 had ACS and 48 had abnormal rCTP. Sensitivity and specificity of rCTP for ACS were 48% (95% confidence interval [CI], 30%–67%) and 78% (95% CI, 71%–85%), respectively. rCTP predicted ACS (adjusted odds ratio, 3.40 [95% CI, 1.37–8.42]; P=0.008) independently of obstructive CAD, and sensitivity for ACS increased from 77% (95% CI, 59%–90%) for obstructive CAD to 90% (95% CI, 74%–98%) with addition of rCTP (P=0.05). In a subgroup undergoing late rest/stress SPECT-MPI (n=81), CCTA/rCTP had noninferior discriminatory value to CCTA/SPECT-MPI (area under the curve, 0.88 versus 0.90; P=0.64) using a noninferiority margin of 10%.

Conclusions—Early rCTP provides incremental value beyond obstructive CAD to detect ACS. CCTA/rCTP is noninferior to CCTA/SPECT-MPI to discriminate ACS and presents an attractive alternative to triage patients presenting with acute chest pain.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00990262.

Key Words: perfusion ◼ emergency service, hospital ◼ tomography, computed ◼ scanners

Coronary computed tomography angiography (CCTA) has emerged in recent years as an effective, efficient, and safe tool in the emergency department (ED) to evaluate low-to-intermediate risk patients with acute chest pain.1,2 Although a completely normal CCTA result provides excellent negative predictive value to exclude acute coronary syndrome (ACS), the sole reliance on the presence of obstructive coronary artery disease (CAD) to identify ACS is less robust.3,4 This can be because of pathophysiologic explanations such as luminal thrombosis followed by recanalization, endothelial dysfunction with decreased coronary flow reserve, and vasospasm.5,6,7 It can also be secondary to technical factors such as image degradation during arrhythmia and inadequate resolution with heavily calcified plaque and branch vessel disease.1,2 In any of these situations, myocardial perfusion assessment can provide complementary physiological data to improve the sensitivity for detecting ACS.

See Clinical Perspective

Earlier studies have presented convincing evidence for the use of myocardial perfusion defects on early resting single-photon emission computed tomography-myocardial perfusion imaging (SPECT-MPI) performed during symptoms for prediction of...
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Prognosis in patients with acute chest pain.13,14 Despite these promising results, most SPECT-MPI in the ED setting is performed after the clinical exclusion of myocardial infarction (MI)/ACS via serial biomarkers and electrocardiography during a 12-hour stay in a chest pain observation unit, in the form of stress and rest SPECT on the following day.2,15–17 This allows for the evaluation of reversible myocardial ischemia, which offers incremental diagnostic value, albeit at the expense of increased time and technical complexity. Moreover, the presence of stress-induced ischemia after serial negative troponins does not completely link the underlying CAD to the presenting symptoms as an ACS. However, resting myocardial ischemia or infarct can also be evaluated on routine clinical CCTA data sets by resting computed tomography perfusion (rCTP), and

Table 1. Patient Demographics and Risk Factors in Patients With and Without ACS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>ACS (n=31)</th>
<th>No ACS (n=152)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.1±12.6</td>
<td>57.3±11.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>23 (74.2)</td>
<td>100 (65.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.8±4.4</td>
<td>29.5±6.2</td>
<td>0.47</td>
</tr>
<tr>
<td>Cardiovascular risk factors (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (64.5)</td>
<td>77 (49.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (16.1)</td>
<td>22 (14.5)</td>
<td>0.78</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>18 (58.1)</td>
<td>75 (49.3)</td>
<td>0.43</td>
</tr>
<tr>
<td>Smoking</td>
<td>17 (54.8)</td>
<td>86 (56.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>No. of CV risk factors, %</td>
<td></td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>0 or 1</td>
<td>35.5</td>
<td>45.4</td>
<td>...</td>
</tr>
<tr>
<td>2 or 3</td>
<td>64.5</td>
<td>50.0</td>
<td>...</td>
</tr>
<tr>
<td>4</td>
<td>0.0</td>
<td>4.6</td>
<td>...</td>
</tr>
<tr>
<td>TIMI score, %</td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>0</td>
<td>12.9</td>
<td>38.8</td>
<td>...</td>
</tr>
<tr>
<td>1</td>
<td>35.5</td>
<td>34.2</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>22.6</td>
<td>21.1</td>
<td>...</td>
</tr>
<tr>
<td>3</td>
<td>29.0</td>
<td>5.9</td>
<td>...</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SD) or as percentages as indicated. ACS indicates acute coronary syndrome; BMI, body mass index; CV, cardiovascular; and TIMI, thrombolysis in myocardial infarction.

*Comparisons between groups were performed with the use of an independent sample t test for continuous variables, Fisher exact test for categorical variables, and the Wilcoxon rank-sum test for ordinal variables.
such studies have shown good diagnostic accuracy in identifying myocardial ischemia and infarct when compared with SPECT-MPI in both the acute\(^{18-20}\) and stable outpatient settings\(^{10,11,21,22}\). For example, Gupta et al\(^{20}\) found that single-phase rCTP analysis had a sensitivity of 91% and specificity of 94% for detection of an irreversible perfusion defect (myocardial infarction) on SPECT-MPI. Similarly, in a cohort of 76 patients presenting with acute chest pain to the ED, Feuchtner et al\(^{18}\) found that rCTP assessment had a sensitivity of 92%, specificity of 95%, positive predictive value of 80%, and negative predictive value (NPV) of 95% on a per-patient level versus late resting SPECT-MPI. In the workup of stable outpatients, stress and rest CTP have been shown to have incremental diagnostic value to identify coronary disease amenable to therapy\(^{23}\).

Based on the results of early resting SPECT-MPI studies in the ED and the excellent agreement of CCTA with SPECT-MPI to identify perfusion deficits under rest/stress, we hypothesized that evaluation of resting myocardial perfusion on early CCTA in patients presenting with acute chest pain to the ED would improve prediction of ACS beyond obstructive CAD assessment. In addition, we hypothesized that early combined assessment of CAD and myocardial perfusion on computed tomography would render excellent agreement with late rest/stress SPECT-MPI performed after clinical rule out of myocardial infarction.

### Methods

#### Study Population

Details of the Rule Out Myocardial Infarction Using Computer-Assisted Tomography (ROMICAT I) observational trial of using CCTA in adults at low-to-intermediate likelihood of ACS presenting to the ED with acute chest pain but without objective signs of myocardial ischemia on initial ECG or necrosis on initial biomarkers have been previously reported. Exclusion criteria included atrial fibrillation, serum creatinine >1.3 mg/dL, and history of CAD.\(^3\)

Of the initial ROMICAT I cohort of 368 patients, we included 183 patients with presence of any CAD by CCTA; flow-chart of exclusion criteria is provided in Figure 1. Therefore, for this secondary analysis, we excluded all patients found to have no plaque on CCTA (ie, those with completely normal coronary arteries), because none of those had ACS.\(^3\) Moreover, we excluded 2 subjects who had incomplete CCTA data sets to permit evaluation of rCTP. The institutional review board approved the study protocol, and all patients provided written informed consent.

#### Coronary Computed Tomography Angiography

The 64-detector-row single-source CCTA protocol in ROMICAT I has previously been described.\(^24\) The presence and extent of coronary atherosclerotic plaque for each coronary segment were determined using a modified 17-segment model of the coronary artery tree. Subjects were classified by blinded expert readers based on the presence and severity of CAD into the following strata: no CAD (no plaque), nonobstructive CAD, and obstructive CAD, and reported previously.\(^3\) Obstructive CAD was defined either as any epicardial coronary artery stenosis with $\geq 50\%$ luminal diameter obstruction or if coronary stenosis could not be confidently excluded (ie, intention-to-diagnose paradigm), whereas nonobstructive CAD was defined as the presence of a coronary artery stenosis $<50\%$.

#### Resting Computed Tomography-Myocardial Perfusion

Special care was used to ensure that readers for rCTP were blinded to coronary artery evaluation images. This was achieved by displaying...
Resting CT Perfusion Improves ACS Prediction

American Heart Association image acquisition guidelines using a standard 1-day rest–stress protocol.29 Patients performed a treadmill exercise protocol or underwent pharmacological stress with intravenous adenosine (Adenoscan, Astellas Pharma US) at 140 μg/kg per minute for ≥3 minutes before radiotracer injection) if unable to exercise. SPECT-MPI was performed after complete serial biomarker and ECG evaluation. The nuclear multplanar reformatted images were analyzed individually by 2 independent readers who were blinded to clinical history, CTA results, and patient outcome, and discrepancies adjudicated by a third reader, as published previously. Analysis was performed in a semiquantitative fashion using a standard American Heart Association 17-segment model and a 5-point scoring system using a commercially available SPECT-MPI image analysis program (4DM SPECT, Ann Arbor, MI).30 Global summed scores were computed for the stress images (summed stress score, reflecting the combined extent and severity of ischemia plus scar) and rest images (summed rest score, reflecting the extent and severity of myocardial scar), as well as their difference (summed difference score, reflecting the combined extent and magnitude of myocardial ischemia). A SPECT-MPI result was considered to be abnormal if the summed stress score was ≥4 or the summed difference score ≥1.30

Definitions of Test Results of Combined CTA/ rCTP and CTA/SPECT-MPI

When both CTA and rCTP were combined as a predictor (CTA/rCTP) for ACS, a positive result was defined as there being either abnormal rest computed tomography perfusion or the presence of obstructive CAD. CTA/rCTP was negative if rCTP was normal, and obstructive CAD was not present on CTA. This decision rule was proposed to optimize sensitivity and NPV for the purpose of more efficient triage of low-to-intermediate risk acute chest pain patients presenting to the ED. However, for completeness, we also assessed the diagnostic test characteristics using an alternate decision rule in which both abnormal rest computed tomography perfusion and obstructive CAD were required to define a positive result: CTA+/rCTP+(4). Similarly, when both CTA and SPECT-MPI were combined as a predictor (CTA/SPECT-MPI) for ACS, a positive result was defined as there being either abnormal SPECT-MPI (summed stress score ≥4 or summed difference score ≥1) or the presence of obstructive CAD. CTA/SPECT-MPI was negative if SPECT-MPI was normal, and obstructive CAD was not present on CTA.

Definition of ACS

The definition of ACS during the index hospitalization in the ROMICAT I cohort has been published previously. Briefly, ACS was defined as either an acute myocardial infarction or unstable angina pectoris. Establishment of this diagnosis was based on an outcome panel of 2 experienced physicians each with >10 years experience who reviewed prospectively collected patient clinical information as well as medical records during the index hospitalization. The outcome panel was blinded to the findings of CTA, and disagreement was resolved by the adjudication of an additional cardiologist.

Statistical Analysis

Baseline demographics of patients with and without ACS were compared with use of independent sample t test for continuous variables, Fisher exact test for categorical variables, and the Wilcoxon rank-sum test for ordinal variables. Continuous variables were expressed as mean±SD; categorical variables were described by frequency. All analyses were performed using Stata (Version 13.1, StatCorp, College Station, TX). A multivariable logistic regression analysis was performed to assess whether rCTP predicted ACS independent of patient characteristics (thrombolysis in myocardial infarction score) and obstructive CAD, and an area under the curve (AUC) analysis was used to determine whether rCTP is incremental to the presence of obstructive CAD.

We compared the combined strategies of CTA/SPECT-MPI and CTA/rCTP for the detection of ACS in a noninferiority analysis.32

Single-Photon Emission Computed Tomography-
Myocardial Perfusion Imaging

The SPECT-MPI protocol and analysis have been previously described by our group.27 Briefly, SPECT-MPI was performed using Tc-99 m-Sestamibi according to the American College of Cardiology/American Heart Association image acquisition guidelines using a standard 1-day rest–stress protocol.29 Patients performed a treadmill exercise protocol or underwent pharmacological stress with intravenous adenosine (Adenoscan, Astellas Pharma US) at 140 μg/kg per minute for ≥3 minutes before radiotracer injection) if unable to exercise. SPECT-MPI was performed after complete serial biomarker and ECG evaluation. The nuclear multplanar reformatted images were analyzed individually by 2 independent readers who were blinded to clinical history, CTA results, and patient outcome, and discrepancies adjudicated by a third reader, as published previously. Analysis was performed in a semiquantitative fashion using a standard American Heart Association 17-segment model and a 5-point scoring system using a commercially available SPECT-MPI image analysis program (4DM SPECT, Ann Arbor, MI).30 Global summed scores were computed for the stress images (summed stress score, reflecting the combined extent and severity of ischemia plus scar) and rest images (summed rest score, reflecting the extent and severity of myocardial scar), as well as their difference (summed difference score, reflecting the combined extent and magnitude of myocardial ischemia). A SPECT-MPI result was considered to be abnormal if the summed stress score was ≥4 or the summed difference score ≥1.30

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Myocardial Perfusion Imaging

The SPECT-MPI protocol and analysis have been previously described by our group.27 Briefly, SPECT-MPI was performed using Tc-99 m-Sestamibi according to the American College of Cardiology/
in the subset of patients who later underwent SPECT-MPI (n=81; Figure 1). Noninferiority was prespecified as a maximal difference of the AUC between a CCTA/SPECT-MPI and CCTA/rCTP strategy of 10%.

### Results

Baseline characteristics of our analytic study cohort (n=183) are shown in Table 1, stratified by outcome of ACS. There were 31 patients with ACS (MI: n=8, unstable angina: n=23), and 152 patients without ACS during the index hospitalization. The thrombolysis in myocardial infarction risk score was significantly higher in the subgroup of patients with ACS during the index hospitalization compared with those without ACS. All 183 patients had CAD by CCTA, among them 67 patients with obstructive CAD (≥50% stenosis). As reported previously, the presence of obstructive CAD by CCTA had a sensitivity of 77% (24/31) for ACS.3

### Resting Computed Tomography-Myocardial Perfusion

For the purpose of this analysis, we dichotomized the rCTP findings into either normal or abnormal (score ≥1). CCTA-based findings of CAD and resting myocardial perfusion in those with and without ACS are depicted in Table 2. rCTP defects were identified in 48 of 183 (26%) patients, with sensitivity for detection of ACS of 48% (15/31) and specificity of 78%. The sensitivity of abnormal rCTP was 38% (3/8) for MI and 52% (12/23) for unstable angina pectoris. The majority of rCTP defects identified in the left anterior descending coronary territory (66%). Among 549 total coronary territories examined (183 patients×3 coronary territories each), there was agreement between abnormal rCTP findings and CCTA-detected obstructive CAD in 75% (410/549) of coronary territories (results not shown). Representative case examples are depicted in Figures 2 to 4.

The overall relationship between abnormal rCTP, obstructive CAD on CCTA, and presence of ACS is displayed in Figure 5. Of note, there were only 3 subjects that would have been missed even with incorporating analysis of rCTP, including 2 with unstable angina and 1 with NSTEMI (Table in the Data Supplement).

In multivariable logistic regression analysis of independent predictors of ACS (adjusted odds ratio, 3.4 [95% CI, 1.4–8.4]; $P=0.008$) after adjusting for obstructive CAD and thrombolysis in myocardial infarction risk score (Table 3). Moreover, combined assessment of CAD and perfusion increased sensitivity of CCTA from 77% (95% CI, 59%–90%) for obstructive CAD alone to 90% (95% CI, 74%–98%) with addition of rCTP ($P=0.05$), using the prespecified decision rule for a positive result being either obstructive CAD or abnormal rCTP). Furthermore, an AUC comparison revealed that abnormal rCTP is incremental to the CCTA presence of obstructive CAD (CCTA: 0.75 [95% CI, 0.66–0.83]; CCTA/rCTP: 0.80 [95% CI, 0.72–0.88]; $P=0.01$) in discriminating the presence from the absence of an ACS. However, this occurred at the expense of decrease in specificity from 72% (for CCTA alone) to 56% (combined; Table 4).

Of note, using the alternate decision of a positive result being both obstructive CAD and abnormal rCTP, specificity

### Table 4. Diagnostic Test Characteristics of Combined CCTA and rCTP Analysis for Prediction of Acute Coronary Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>Balanced Accuracy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCTA(+)</td>
<td>77.4 (58.9–90.4)</td>
<td>71.7 (63.8–78.7)</td>
<td>35.8 (24.5–48.5)</td>
<td>94.0 (88.0–97.5)</td>
<td>74.6 (66.3–82.9)</td>
</tr>
<tr>
<td>rCTP(+)</td>
<td>48.4 (30.2–66.9)</td>
<td>78.3 (70.9–84.6)</td>
<td>31.3 (18.7–46.3)</td>
<td>88.1 (81.5–93.1)</td>
<td>63.3 (53.8–72.9)</td>
</tr>
<tr>
<td>CCTA(+) or rCTP(+)</td>
<td>90.3 (74.2–98.0)</td>
<td>55.9 (47.6–64.0)</td>
<td>29.5 (20.6–39.7)</td>
<td>96.6 (90.4–99.3)</td>
<td>73.1 (66.5–79.7)</td>
</tr>
<tr>
<td>CCTA(+) and rCTP(+)</td>
<td>35.5 (19.2–54.6)</td>
<td>94.1 (89.1–97.3)</td>
<td>55.0 (31.5–76.9)</td>
<td>87.7 (81.7–92.3)</td>
<td>64.8 (56.0–73.5)</td>
</tr>
</tbody>
</table>

*Balanced accuracy=0.5×(Sensitivity+Specificity)=area under the curve.
Resting CT Perfusion Improves ACS Prediction

Table 6. Diagnostic Accuracy of CCTA, rCTP, and Combined Predictors for Acute Coronary Syndrome in the 81 Subjects Undergoing Later SPECT-Myocardial Perfusion Imaging

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>Balanced Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCTA(+)</td>
<td>92.3 (64.0–99.8)</td>
<td>70.6 (68.3–81.0)</td>
<td>37.5 (21.1–56.3)</td>
<td>98.0 (89.1–99.9)</td>
<td>81.4 (72.1–90.8)</td>
</tr>
<tr>
<td>rCTP(+)</td>
<td>53.8 (25.1–80.8)</td>
<td>75.0 (63.0–84.7)</td>
<td>29.2 (12.6–51.1)</td>
<td>89.5 (78.5–96.0)</td>
<td>64.4 (49.4–79.4)</td>
</tr>
<tr>
<td>SPECT(+)</td>
<td>69.2 (38.6–90.9)</td>
<td>88.2 (78.1–94.8)</td>
<td>52.9 (27.8–77.0)</td>
<td>93.8 (84.8–98.3)</td>
<td>78.7 (65.1–92.3)</td>
</tr>
<tr>
<td>CCTA(+) or rCTP(+)</td>
<td>100.0 (75.3–100.0)</td>
<td>50.0 (37.6–62.4)</td>
<td>27.7 (15.6–42.6)</td>
<td>100.0 (89.7–100.0)</td>
<td>75.0 (69.0–81.0)</td>
</tr>
<tr>
<td>CCTA(+) or SPECT(+)</td>
<td>92.3 (64.0–99.8)</td>
<td>61.8 (49.2–73.3)</td>
<td>31.6 (17.5–48.7)</td>
<td>97.7 (87.7–99.9)</td>
<td>77.0 (67.5–86.6)</td>
</tr>
</tbody>
</table>

SPECT(+) if summed stress score ≥4 or summed difference score ≥1. CCTA indicates coronary computed tomography angiography; CCTA(+), obstructive (≥50%) or indeterminate; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; rCTP, resting computed tomography perfusion; rCTP(+), possible perfusion defect (score ≥1); and SPECT, single-photon emission computed tomography.

Discussion

Our findings demonstrate that early rCTP analysis provides incremental value for prediction of ACS to obstructive CAD assessment by CCTA in low-to-intermediate risk patients presenting to the ED. In addition, a combined early CCTA and rCTP analysis is noninferior to CCTA and late (after exclusion of MI) SPECT-MPI to predict ACS. Hence, comprehensive early CCTA including rest perfusion assessment has the potential to improve efficiency of CCTA in a safe manner without additional cost, infrastructure, radiation exposure, or contrast administration.

Our findings are consistent with previous trials of SPECT-MPI in the ACS exclusion setting demonstrating safe triage and high accuracy for ACS diagnosis, when testing was performed as early as possible after ED presentation. Our results support the concept that analysis of computed tomography resting first pass perfusion during initial chest pain evaluation provides incremental value to anatomic CTA data to include or exclude ACS.13 The current study also extends previous work by our group and others in evaluating resting perfusion defects in smaller cohorts of higher risk patients with acute chest pain.33–35 In comparison with these studies in which the majority had ACS and underwent cardiac catheterization, our study cohort was at low to intermediate risk for ACS. However, a recent study by Branch et al36 represents a similar patient population (9 ACS events in 105 patients). However, they had only 3 patients with abnormal resting perfusion and showed improved specificity but reduced sensitivity when added to stenosis assessment. In contrast, we had a more granular assessment of myocardial perfusion abnormality (reporting on a 1–3 scale of confidence in there being a true perfusion defect) and therefore had more patients with abnormal perfusion, and our focus was on improving triage of patients with CAD in the ED setting or optimizing sensitivity and NPV rather than specificity.

Overall, our results suggest that combined CCTA/rCTP is noninferior to CCTA/SPECT-MPI to discriminate ACS and hence presents an attractive alternative to accurately triage and manage patients presenting with acute chest pain to the ED found to have any plaque by CCTA. (Those without any plaque were shown to have a 0% ACS and hence were not part of this study cohort.) The improved sensitivity/ NPV of CCTA/rCTP would result in less missed ACS cases being discharged to home. In addition, the noninferiority of CCTA/rCTP to CCTA/SPECT-MPI for detection of ACS (based upon AUC) suggests that assessment of rCTP in our cohort would be an efficient use of resources without the additional cost and radiation exposure of sequential diagnostic testing.

However, our study is not without limitations. Our cohort is modest in size, with a relatively small number of events, particularly in our subgroup analysis. Nevertheless, our outcomes were adjudicated events that were independent of any findings on CCTA, and we succeeded to show noninferiority of combined CCTA/rCTP compared with CCTA/SPECT-MPI. In addition, the ROMICAT I participants were recruited between 2005 and 2007, and CCTA technical parameters have significantly improved during the past several years. For example, arrhythmia, calcium burden, and even renal insufficiency play a decreasing role in CCTA contraindications in the era of dual-source computed tomography, arrhythmia rejection algorithms, single-heartbeat imaging, and iterative reconstruction algorithms. However, the ROMICAT I cohort was performed with 64-detector-row CCTA, which is still considered an acceptable minimum standard for clinical CCTA.

was increased from 72% (95% CI, 64–79) to 94% (95% CI: 89–97), at the expense of significantly reduced sensitivity of only 36% (95% CI, 19–55).

Substudy Comparison of rCTP to SPECT-MPI

Among the subset of patients who underwent SPECT-MPI (n=81), 13 subjects had ACS. Diagnostic test results stratified by ACS outcome and test accuracy are shown in Tables 5 and 6. CCTA/rCTP had a sensitivity of 100%, specificity of 50%, NPV of 98%, and positive predictive value of 28% for the detection of ACS in this subgroup. CCTA/SPECT-MPI had a sensitivity of 92%, specificity of 62%, NPV of 100%, and positive predictive value of 32% for the detection of ACS in this subgroup.

To test whether CCTA/rCTP is noninferior to CCTA/ SPECT-MPI for the detection of ACS, we compared the AUC for both strategies. The AUC for CCTA/SPECT-MPI was 0.88 (95% CI, 0.81–0.96), and the AUC for CCTA/rCTP was 0.90 (95% CI, 0.79–1.00). Therefore, the AUC analysis met the prespecified margin of noninferiority between the strategies of 10% (ie, the lower bound of the CI of CCTA/rCTP, 0.79, exceeded the noninferiority threshold of 0.78=0.88–0.10).

Discussion

Our findings demonstrate that early rCTP analysis provides incremental value for prediction of ACS to obstructive CAD assessment by CCTA in low-to-intermediate risk patients presenting to the ED. In addition, a combined early CCTA and rCTP analysis is noninferior to CCTA and late (after exclusion of MI) SPECT-MPI to predict ACS. Hence, comprehensive early CCTA including rest perfusion assessment has the potential to improve efficiency of CCTA in a safe manner without additional cost, infrastructure, radiation exposure, or contrast administration.

Our findings are consistent with previous trials of SPECT-MPI in the ACS exclusion setting demonstrating safe triage and high accuracy for ACS diagnosis, when testing was performed as early as possible after ED presentation. Our results support the concept that analysis of computed tomography resting first pass perfusion during initial chest pain evaluation provides incremental value to anatomic CTA data to include or exclude ACS.13 The current study also extends previous work by our group and others in evaluating resting perfusion defects in smaller cohorts of higher risk patients with acute chest pain.33–35 In comparison with these studies in which the majority had ACS and underwent cardiac catheterization, our study cohort was at low to intermediate risk for ACS. However, a recent study by Branch et al36 represents a similar patient population (9 ACS events in 105 patients). However, they had only 3 patients with abnormal resting perfusion and showed improved specificity but reduced sensitivity when added to stenosis assessment. In contrast, we had a more granular assessment of myocardial perfusion abnormality (reporting on a 1–3 scale of confidence in there being a true perfusion defect) and therefore had more patients with abnormal perfusion, and our focus was on improving triage of patients with CAD in the ED setting or optimizing sensitivity and NPV rather than specificity.

Overall, our results suggest that combined CCTA/rCTP is noninferior to CCTA/SPECT-MPI to discriminate ACS and hence presents an attractive alternative to accurately triage and manage patients presenting with acute chest pain to the ED found to have any plaque by CCTA. (Those without any plaque were shown to have a 0% ACS and hence were not part of this study cohort.) The improved sensitivity/ NPV of CCTA/rCTP would result in less missed ACS cases being discharged to home. In addition, the noninferiority of CCTA/rCTP to CCTA/SPECT-MPI for detection of ACS (based upon AUC) suggests that assessment of rCTP in our cohort would be an efficient use of resources without the additional cost and radiation exposure of sequential diagnostic testing.

However, our study is not without limitations. Our cohort is modest in size, with a relatively small number of events, particularly in our subgroup analysis. Nevertheless, our outcomes were adjudicated events that were independent of any findings on CCTA, and we succeeded to show noninferiority of combined CCTA/rCTP compared with CCTA/ SPECT-MPI. In addition, the ROMICAT I participants were recruited between 2005 and 2007, and CCTA technical parameters have significantly improved during the past several years. For example, arrhythmia, calcium burden, and even renal insufficiency play a decreasing role in CCTA contraindications in the era of dual-source computed tomography, arrhythmia rejection algorithms, single-heartbeat imaging, and iterative reconstruction algorithms. However, the ROMICAT I cohort was performed with 64-detector-row CCTA, which is still considered an acceptable minimum standard for clinical CCTA.
Several adjunctive techniques have emerged in recent times that promise to offer improvements in the diagnostic profile of traditional CCTA. Each of these is not without limitations, but merit discussion and evaluation, particularly with an eye toward a practical implementation in the acute chest pain population. Perhaps the most widely publicized development is fractional flow reserve with computed tomography using computational fluid dynamic modeling to predict the hemodynamic consequence of anatomic lesions. Although initial results were only somewhat comforting, additional generations of the proprietary algorithm have demonstrated improved results.37–39 However, this method demands pristine data sets and requires off-site processing by experts and high-level processing workstations, thus eliminating the possibility of timely disposition decisions based on results in the ED setting. Stress and rest perfusion computed tomography is a second promising technique, but with it come all the practical limitations of stress and rest SPECT-MPI in the ED setting: for safety reasons, most hospitals require >1 set of cardiac enzymes and ECG before allowing a patient to proceed to a stress examination, given concerns for ischemia even with pharmacological stress (in the past years pharmacological stress agents have even been issued black box warnings by the Food and Drug Administration because of concerns for causing ischemia in rare cases). Dual energy has been proposed as a potential answer to resting (and stress) perfusion, while this technique may alleviate some issues by allowing a more quantitative evaluation of myocardial enhancement; it is neither widely available on all platforms nor validated to independently improve diagnostic perfusion evaluation beyond single-energy CTP. Additional methodologies such as wide-area-detectors, advanced iterative reconstructions and beam-hardening corrections, and even spectral computed tomography are available or on the horizon, but none are yet validated across multiple vendor platforms. Thus, although our cohort was scanned on relatively common and decidedly aging computed tomography technology, we feel that our cohort represents a reasonable minimum standard for modern ED CCTA practice.

In the era of radiation dose reduction, cost containment, and increasing use of prospective ECG-triggering (thus forgoing the potential for wall motion analysis), our findings are of particular interest. However, further larger scale studies including randomized controlled trials are necessary to confirm our findings and apply them to other populations of patients.

Conclusions

Early rCTP provides incremental value beyond obstructive CAD to detect ACS. Combined CCTA/rCTP is noninferior to CCTA/SPECT-MPI to discriminate ACS and hence presents an attractive alternative to accurately triage and manage patients presenting with acute chest pain to the ED.

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Disclosures

None.

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Resting CT Perfusion Improves ACS Prediction

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CLINICAL PERSPECTIVE

Prior studies have shown excellent agreement between rest/stress computed tomography perfusion and single-photon emission computed tomography-myocardial perfusion imaging, but the value of resting computed tomography perfusion analysis in acute chest pain triage remains unclear. Controversy remains as to whether such evaluation provides incremental value to stenosis evaluation by coronary computed tomography angiography (CCTA) to include or exclude acute coronary syndrome. In this secondary analysis of the observational Rule Out Myocardial Infarction with Computer-Assisted Tomography (ROMICAT)-I trial of low-to-intermediate risk patients presenting to the emergency department with symptoms suggestive of acute coronary syndrome underwent CCTA with results blinded to providers and were therefore managed according to standard clinical care. We found that assessment of resting myocardial computed tomography perfusion in those patients with any plaque on CCTA provided independent and incremental value beyond coronary stenosis and also increased the sensitivity for detection of acute coronary syndrome. Hence, comprehensive early CCTA including rest perfusion assessment has the potential to improve efficiency of CCTA in a safe manner without additional cost, infrastructure, radiation exposure, or contrast administration.
Early Resting Myocardial Computed Tomography Perfusion for the Detection of Acute Coronary Syndrome in Patients With Coronary Artery Disease
Amit Pursnani, Ashley M. Lee, Thomas Mayrhofer, Waleed Ahmed, Shanmugam Uthamalingam, Maros Ferencik, Stefan B. Puchner, Fabian Bamberg, Christopher L. Schlett, James Udelson, Udo Hoffmann and Brian B. Ghoshhajra

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**Supplemental Material**

**Supplemental Table.** Detailed Information on Results of Standard Care in Subjects Who were Determined to have ACS with normal rCTP (score=0) and Non-Obstructive CAD on CCTA

<table>
<thead>
<tr>
<th>Subject</th>
<th>CCTA Finding of Non-obstructive Plaque</th>
<th>Baseline ECG</th>
<th>Troponin</th>
<th>Stress Nuclear Perfusion Imaging</th>
<th>Coronary Angiography Intervention</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>72-year-old man</td>
<td>Mid-RCA</td>
<td>Non-specific T-wave changes</td>
<td>Negative</td>
<td>Apical area of ischemia, hypokinesis inferolateral region</td>
<td>None</td>
<td>Unstable Angina</td>
</tr>
<tr>
<td>53-year-old man</td>
<td>LM and distal LAD</td>
<td>Non-specific T-wave changes</td>
<td>2nd set positive</td>
<td>None</td>
<td>40% D2 ostium, 70% D3 ostium stenosis/ none</td>
<td>NSTEMI</td>
</tr>
<tr>
<td>59-year-old woman</td>
<td>OM1</td>
<td>&lt;1mm ST-segment elevation V2-V6</td>
<td>Negative</td>
<td>None</td>
<td>80% PDA stenosis/stent PDA</td>
<td>Unstable Angina</td>
</tr>
</tbody>
</table>

D2=second diagonal branch; D3= third diagonal branch; NSTEMI= Non-ST segment myocardial infarction; PDA=posterior descending artery