Rates of downstream invasive coronary angiography and revascularization: computed tomographic coronary angiography vs. Tc-99m single photon emission computed tomography

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Aims
Computed tomographic coronary angiography (CTA) appears to be a useful modality for the detection of obstructive coronary artery disease (CAD). Recent data suggest that CTA may reduce the frequency of normal invasive coronary angiograms. However, there remains concern that the implementation of CTA could increase referrals to invasive coronary angiography (ICA). To further support the clinical acceptance of CTA, it is important to compare CTA to another accepted modality such as single photon emission computed tomography (SPECT). We followed a cohort of 64-slice CTA patients and a matched cohort of Tc-99m SPECT patients to determine downstream referrals for ICA and revascularization.

Methods and results
Consecutive CTA patients (without history of revascularization or cardiac transplantation) were prospectively enrolled and compared with a Tc-99m SPECT cohort (matched for age, gender, and Morise score). Each CTA and SPECT was evaluated for obstructive CAD and patients were followed for downstream ICA and revascularization. Of the 1221 patients in each cohort, 129 (10.6%) CTA patients and 125 (10.2%) SPECT patients were referred to ICA. Of those referred to ICA, obstructive CAD was confirmed in 105 (81.4%) CTA patients and in 88 (70.4%) SPECT patients. Differences in false positive rates were significantly lower in the CTA than the SPECT cohort (9.7 and 25.8%, respectively, \(P = 0.009\)). Rates of revascularization were similar in the CTA and SPECT cohorts (6.2 vs. 5.9%, respectively).

Conclusion
Compared with SPECT, CTA had similar referrals for ICA and revascularization rates but lower false positive rates. Computed tomographic coronary angiography appears to be a viable non-invasive diagnostic modality and does not appear to negatively impact upon ICA resources.

Keywords
Computed tomography • Coronary angiography • Revascularization • SPECT • Myocardial perfusion imaging

Introduction
Computed tomographic coronary angiography (CTA) is a useful non-invasive diagnostic and prognostic tool for the detection and exclusion of obstructive coronary artery disease (CAD).1–11 Our centre previously demonstrated that the implementation of a cardiac CT laboratory resulted in the reduction in the frequency of ‘normal’ invasive coronary angiograms.10 Though promising, the clinical impact of CTA on invasive coronary angiography (ICA) resource utilization has not been fully understood.12 What remains unclear is the downstream utilization of ICA and rate of revascularization of patients after CTA and how this might directly

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Methods

Between February 2006 and January 2009, consecutive CTA patients with suspected CAD were prospectively enrolled into an observational Cardiac CT Registry and were followed for ICA and coronary revascularization. Computed tomographic coronary angiography patients with prior SPECT or ICA, history of CAD or prior coronary revascularization, or cardiac transplantation were excluded from the analysis. Also excluded were patients participating in research where ICA was mandated (regardless of CTA result).

To ensure comparable groups, a control cohort of Tc-99m SPECT patients was selected from 17,417 Tc-99m SPECT studies performed in patients with suspected CAD during the same time period as CTA. Single photon emission computed tomography patients were selected by individually matching each CTA case using major characteristics (age, gender, and Morise score). Similar exclusion criteria were used in the SPECT cohort. To ensure that the CTA and SPECT cohorts were non-overlapping, SPECT patients with a preceding CTA were also excluded. If a CTA case matched more than one control, a single control was randomly selected. Rates of ICA and revascularization were assessed in this matched cohort and compared with the CTA cohort. The study was approved by the Institutional Human Research Ethics Board and all patients provided written informed consent.

Clinical predictors

At the time of CTA and SPECT, a detailed medical history was recorded for all patients. Pre-test probability for obstructive CAD was calculated for individual patients using age, gender, and symptoms. The Morise score (based upon pre-test probability and cardiac risk factors) was calculated for both groups.

CT coronary angiography

Before CTA acquisition, metoprolol or diltiazem was administered targeting a heart rate of ≤65 b.p.m. Nitroglycerin (0.8 mg) was given sublingually, provided there were no contraindications. A biphasic timing bolus method was utilized [Visipaque 320 or Omnipaque 350 (GE Healthcare, Princeton, New Jersey)] and a triphasic protocol was used to acquire the final CTA data set. The GE Volume CT (GE, Milwaukee, Wisconsin) with 64 × 0.625 mm slice collimation and a gantry rotation of 350 ms (mA = 400–800, kV = 120) was used to acquire retrospective ECG-gated data sets using ECG-gated X-ray tube modulation. The cardiac phase(s) with the least amount of motion was used for the interpretation of coronary anatomy.

Computed tomographic coronary angiography image analysis

The GE Advantage Volume Share Workstation (GE, Milwaukee, Wisconsin) was used for post-processing and data sets were interpreted by expert observers blinded to all clinical data. Coronary stenoses were evaluated using a 17 segment model of the coronary arteries and 4-point grading score [normal, mild (<50%), moderate (50–69%), severe (>70%)]. Obstructive CAD was defined as lesions with ≥50% diameter stenosis.

Tc-99 single photon emission computed tomography

Tc-99m (tetrofosmin) SPECT myocardial perfusion imaging was performed and reported as per clinical routine and guidelines. In brief, a 1-day rest-stress (exercise or dipyridamole) protocol was used. Images were acquired on dual-headed cameras using low-energy high-resolution collimators and a 15% energy window centred on the 140 keV photopeak. ECG-gated SPECT data were acquired (25 s/project × 60 projections over 180°) and reconstructed with filtered back-projection using a 64 × 64 matrix. Single photon emission computed tomography images were reviewed by expert observers using a standardized reporting template. All results were categorized as normal or abnormal based upon the stress electrocardiogram, myocardial perfusion, ventricular wall motion, ejection fraction, and other features such as transient ischaemic dilatation. SPECT reports were retrospectively collected and carefully reviewed. For the purposes of this study, patients were considered abnormal if the image interpretation was consistent with obstructive CAD.

Patient follow-up

Based upon CTA and SPECT results, patients were categorized into no obstructive CAD and obstructive CAD. To understand the direct impact of CTA and SPECT upon ICA and false positive rates, patients were followed for ICA and revascularization within 6 months of their test. Computed tomographic coronary angiography patients were also followed for cardiac death and non-fatal myocardial infarction. Patient follow-up was performed by telephone interview and using the local coronary angiogram database. All events were confirmed with death records, hospital records, or correspondence with treating physicians.

Statistical analysis

Statistical analyses were performed using SAS (version 9.2, SAS Institute Inc., Cary, NC, USA), and statistical significance was defined as P < 0.05. Continuous variables are presented as means and standard deviations, continuous variables not normally distributed are presented as medians and interquartile range, and categorical variables are presented as frequencies with percentages. The conditional logistic regression was used to compare the patient characteristics, ICA referral and revascularization rates between pair-matched CTA and SPECT patients. Diagnostic test characteristics (sensitivity, specificity, positive predictive value, and negative predictive value) were reported with 95% confidence intervals (CI). The agreement of CTA and SPECT with ICA was evaluated using Kappa statistics.

Results

Over an enrolment period of 36 months, 3957 consecutive patients underwent CTA with a total of 3935 (99.4%) patients prospectively enrolled into the University of Ottawa Heart Institute [University of Ottawa Heart Institute (UOHI)] servicing a large population, our centre is in a unique position to accurately assess ICA referrals and revascularization decisions after cardiac CT and SPECT. To further support the clinical acceptance of CTA, we sought to compare a matched cohort of CTA and SPECT patients to understand rates of referral to ICA, revascularization, and false positive results.

Comparing to an accepted modality such as Tc-99m single photon emission computed tomography (SPECT). Since cardiac CT and cardiac catheterization services are centralized to a single tertiary-care centre [University of Ottawa Heart Institute (UOHI)] servicing a large population, our centre is in a unique position to accurately assess ICA referrals and revascularization decisions after cardiac CT and SPECT.

Before CTA acquisition, metoprolol or diltiazem was administered sublingually, provided there were no contraindications. A biphasic timing bolus method was utilized [Visipaque 320 or Omnipaque 350 (GE Healthcare, Princeton, New Jersey)] and a triphasic protocol was used to acquire the final CTA data set. The GE Volume CT (GE, Milwaukee, Wisconsin) with 64 × 0.625 mm slice collimation and a gantry rotation of 350 ms (mA = 400–800, kV = 120) was used to acquire retrospective ECG-gated data sets using ECG-gated X-ray tube modulation. The cardiac phase(s) with the least amount of motion was used for the interpretation of coronary anatomy.

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To ensure comparable groups, a control cohort of Tc-99m SPECT patients was selected from 17,417 Tc-99m SPECT studies performed in patients with suspected CAD during the same time period as CTA. Single photon emission computed tomography patients were selected by individually matching each CTA case using major characteristics (age, gender, and Morise score). Similar exclusion criteria were used in the SPECT cohort. To ensure that the CTA and SPECT cohorts were non-overlapping, SPECT patients with a preceding CTA were also excluded. If a CTA case matched more than one control, a single control was randomly selected. Rates of ICA and revascularization were assessed in this matched cohort and compared with the CTA cohort. The study was approved by the Institutional Human Research Ethics Board and all patients provided written informed consent.
Table 1  Comparisons between pair-matched computed tomographic coronary angiography and single photon emission computed tomography cohorts

<table>
<thead>
<tr>
<th>Matched characteristics</th>
<th>CTA (n = 1221)</th>
<th>Tc-99m SPECT (n = 1221)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morise score</td>
<td>10.7 ± 3.0</td>
<td>10.7 ± 3.0</td>
<td>1.000</td>
</tr>
<tr>
<td>Age</td>
<td>58.1 ± 10.9</td>
<td>58.1 ± 10.9</td>
<td>1.000</td>
</tr>
<tr>
<td>Male</td>
<td>622 (50.9%)</td>
<td>622 (50.9%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Radiation exposure (mSv)</td>
<td>14.9 (13.1, 17.1)</td>
<td>10.5 (10.1, 11.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>22.0 (15.0, 28.0)</td>
<td>24.0 (16.0, 33.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-test probability of CAD</td>
<td>12.3 (7.0, 22.0)</td>
<td>12.3 (7.5, 31.0)</td>
<td>0.511</td>
</tr>
<tr>
<td>Body mass index (BMI; kg/m²)</td>
<td>27.0 (24.0, 31.0)</td>
<td>28.0 (25.0, 31.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>Baseline heart rate</td>
<td>66 (59, 74)</td>
<td>66 (59, 75)</td>
<td>0.849</td>
</tr>
<tr>
<td>Baseline blood pressure</td>
<td>135 (123, 150)/79 (72, 86)</td>
<td>140 (128, 158)/84 (78, 90)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cardiac risk factors
- Diabetes
- Hypertension
- Dyslipidaemia
- Current/history of smoking
- Family history of CAD

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>CTA</th>
<th>Tc-99m SPECT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>620 (50.8%)</td>
<td>596 (48.8%)</td>
<td>0.331</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac medications</th>
<th>CTA</th>
<th>Tc-99m SPECT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I</td>
<td>263 (21.5%)</td>
<td>355 (29.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>623 (51.0%)</td>
<td>486 (39.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>424 (34.7%)</td>
<td>274 (22.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>431 (35.3%)</td>
<td>438 (35.9%)</td>
<td>0.767</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin converting enzyme-inhibitor; CAD, coronary artery disease; CTA, computed tomographic coronary angiography; SPECT, single photon emission computed tomography.

Institute Cardiac CT Registry. Of these, 2714 patients were excluded for a history of CAD or previous coronary revascularization (737 patients), any prior SPECT testing (1075 patients), previous ICA and/or participation in ICA research (656 patients), or history of cardiac transplantation (27 patients). Another 219 patients could not be matched to the SPECT cohort. The remaining 1221 patients (mean age 58.1 ± 10.9 years; men = 50.9%; Morise score = 10.7 ± 3.0) met the inclusion criteria for this study. A matched SPECT cohort (1221 patients, mean age = 58.1 ± 10.9 years; men = 50.9%; Morise score = 10.7 ± 3.0) was selected for comparison (Table 1). Though matched, the SPECT cohort had a greater body mass index, and higher baseline blood pressures, but lower incidence of dyslipidaemia, smoking history, and family history of CAD. Of the 1221 SPECT scans, there were a total of 231 (18.9%) abnormal and 24 (2.0%) equivocal scans. Of the 1221 CT scans, there were a total of 300 (24.6%) showing obstructive CAD. Since CTA used ‘forced reading’, the total number of equivocal studies was not documented, but <3.0% of segments were unevaluable due to small vessel size, cardiac motion, or severe calcification. Invasive coronary angiography follow-up duration was slightly longer in the SPECT than the CTA group (24.7 ± 10.0 vs. 21.8 ± 8.8 months, respectively).

Referral to invasive coronary angiography and revascularization

Of the CTA and SPECT cohorts, a total of 129 (10.6%) CTA and 125 (10.2%) SPECT patients were referred to ICA (P = 0.791) (Table 2). Of the patients who underwent ICA, obstructive CAD was confirmed in 105 (81.4%) of CTA and 88 (70.4%) of Tc-99m SPECT patients. In the CTA cohort, 76 of the 1221 (6.2%) patients underwent coronary revascularization procedures (48 PCI and 23 CABG) and was similar to the SPECT cohort in which 72 (5.9%) patients underwent coronary revascularization procedures (49 PCI and 23 CABG) (P = 0.832). The revascularization rates in CTA patients with confirmed obstructive CAD (72.4%) was similar to revascularization rate in SPECT patients (81.8%; P = 0.123). A total of 29 CTA patients with confirmed obstructive CAD were treated medically. During follow-up of the 129 CTA patients referred for ICA, there was 1 cardiac death and 5 non-fatal myocardial infarctions.

In the SPECT group, 16 patients with confirmed obstructive CAD did not undergo revascularization. Medical therapy was recommended for 14 patients and 2 patients declined revascularization. Differences in false positive rates (abnormal CTA or SPECT but ICA <50% stenosis) were significantly lower in the CTA than the SPECT cohort (9.7 and 25.8%, respectively, P = 0.009).
Of all the CTA and SPECT patients referred to ICA, obstructive CAD was excluded in 24 (18.6%) CTA and 37 (29.6%) SPECT patients. The sensitivity and specificity of CTA in detecting obstructive CAD was 97.1% (CI: 91.3–99.3%) and 54.2% (CI: 33.2–73.8%), respectively. The sensitivity and specificity of SPECT in detecting obstructive CAD was 81.8% (CI: 71.9–88.9%) and 32.4% (CI: 18.6–49.9%), respectively. The positive and negative predictive values of CTA and SPECT were 90.3% (CI: 82.9–94.8%) and 81.3% (CI: 53.7–95.0%), and 74.2% (CI: 64.2–82.3%) and 42.9% (CI: 25.0–62.6%), respectively (Table 3). The agreement between CTA and ICA was 0.59 (CI: 0.39–0.79) and between SPECT and ICA was 0.15 (CI: −0.00–0.37).

Of the remaining 1094 CTA patients who were not referred for ICA within 6 months follow-up was available for 96.1% of patients. During follow-up, there were two cardiac deaths (one patient had significant two vessel disease treated medically, and the other patient had severe pulmonary hypertension with RV dysfunction) and one non-fatal myocardial infarction.

## Discussion

The results of our study suggest that, when compared with SPECT, CTA did not result in increased referrals for ICA. The false positive rates were significantly lower in the CTA than the SPECT cohort (9.7 and 25.8%, respectively, \( P = 0.009 \)). Though the two populations were matched for age, gender, and Morise score, there were variations in cardiac risk factors which may have influenced ICA referral patterns.
To date, there is limited data detailing the impact of CTA upon downstream resource utilization, referrals to ICA and revascularization. Our centre previously reported that the implementation of a cardiac computed tomography program was associated with a reduction in the rate of ‘normal’ angiograms compared with historical and case controls and that CTA has prognostic value. However, the true impact of a CTA upon ICA and its comparison to an existing modality has never been formally assessed. A better understanding of downstream ICA, revascularization, and patient outcomes after CTA compared with SPECT is required to ensure that CTA does not lead to excessive and inappropriate ICA. The results of our study confirm that CTA and SPECT have similar rates of ICA and revascularization with CTA having fewer false positives.

To understand the potential role of CTA in the detection of CAD, one needs to understand the strengths and weaknesses of CTA as well as those of other available modalities. Single photon emission computed tomography is widely available and commonly used for detecting the presence and severity of myocardial ischaemia. Single photon emission computed tomography has been shown to have reliable operating characteristics with a sensitivity of 86% and specificity of 74%. Studies have demonstrated the independent and incremental prognostic value of functional imaging with SPECT over clinical and anatomical measures. However, SPECT cannot delineate coronary anatomy nor non-obstructive atherosclerotic plaque. Conversely, a potential strength of CTA is its ability to accurately detect and localize subclinical coronary atherosclerosis which may have incremental prognostic value.

There is growing concern in regards to the radiation exposure associated with medical imaging such as CTA and SPECT. Current single day Tc-99m SPECT delivers a radiation dose of 9–11 mSv however, these doses will likely fall with the adoption of newer technologies using cadmium zinc telluride detectors. Similarly, CTA exposes patients to ionizing radiation but techniques are being adopted to reduce patient radiation exposure. Though retrospective ECG-gated image acquisition (with ECG-gated tube modulation) was used in our study cohort, most centres have since adopted prospective triggering thus reducing the amount of radiation delivered to a mere fraction of original CTA doses. Many centres with ‘state-of-the-art’ scanners are now reporting doses <1 mSv which are much lower than those of SPECT.

The limitations of anatomical imaging raise concerns that an over-reliance on ‘coronary anatomy’ may result in excessive ICAs and that the ‘oculo-stenotic reflex’ will increase revascularization procedures. The results of our study suggest that this may not be the case since the rates of revascularization appeared to be similar between CTA and SPECT.

Acceptance of an imaging modality into clinical practice typically results in referral and verification bias. Since ‘abnormal’ studies are more commonly referred to ICA than ‘normal’ studies, a reduction in specificity is commonly observed. As expected, this bias was observed in both the CTA and SPECT cohorts. Recognizing the discrepancies between anatomical and functional testing, the accuracy and agreements of the two modalities cannot be directly compared. However, since both tests function as gatekeepers for ICA, the frequency of inappropriate referrals to ICA may be indirectly estimated using false positive rates. To ensure appropriate healthcare resource utilization, clinicians endeavour to minimize the referring of patients with non-obstructive CAD for ICA. Thus, an abnormal CTA or SPECT in patients without obstructive CAD is undesirable. The results of our study suggest that such cases (false positives) are lower with CTA than SPECT.

At first glance, CTA appears to have better operating characteristics and agreement with ICA than SPECT. However, the discordance between anatomy and function has been well studied and thus definitive conclusions regarding the accuracy of CTA compared with SPECT should be dissuaded. Since only a small proportion of our population was referred to ICA, the calculated operating characteristics are subject to population bias. The results do confirm the disagreement between functional assessment with SPECT and anatomical measures using ICA. The results of our study do reassure clinicians that ICA rates are similar between the two modalities. However, large randomized controlled studies are needed to fully understand the potential impact of CTA compared with SPECT.

The cost-effectiveness of CTA and SPECT was recently examined by Min et al. Using a decision analysis, they demonstrated that for a 55-year-old man with a pre-test probability of 30%, a CTA strategy was more cost-effective than a SPECT strategy. If the cost of CTA is lower than SPECT, our study results would support the notion that CTA may be more cost-efficient than SPECT.

**Limitations**

This was a prospective observational CTA single centre study. The results of this study may not be uniformly translated to all other centres due to variability in experience and practice between institutions and countries. This study utilizes a matched SPECT cohort for comparison, thus the strength of the results is limited if the cohorts cannot be perfectly matched. As well, our study could not identify specific populations that would benefit most from CTA rather than SPECT and vice versa. These limitations may be overcome in the future by randomized controlled trials. Since this was a single centre study with a lower pre-test probability for CAD, the results of our study may not necessarily reflect the patient population or physician practice at other centres. Though all CTA and SPECT studies were performed and interpreted at the same institution, image interpretation and recommendations were left to the discretion of the interpreting physician, which could result in bias. Similarly, patient referrals and downstream investigations and treatment were left to the discretion of the treating physicians, which could also be a source of bias. Though this study could not identify ‘false negative’ CTAs, patients were followed for major adverse events, and the low event rates are reassuring. Though follow-up for the SPECT population was not available, it was beyond the scope of this study. Downstream SPECT after CTA or CTA after SPECT may also be confounders. Within 2 months after CTA, 68 (5.6%) patients went on to SPECT and similarly, 47 (3.8%) SPECT patients underwent CTA with only 11 CTA and 9 SPECT patients referred to ICA. Since this population is small, the incremental value of combining CTA + SPECT could not be assessed.
Large multicentre prospective cohort studies such as ‘the study of myocardial perfusion and coronary anatomy imaging roles in CAD (SPARC)’ with extended follow-up are required to fully comprehend the downstream utilization of all resources after CTA and SPECT. Such studies will enable us to understand potential limitations of these tests in various populations and may permit us to better tailor test selection according to patient characteristics.

We also recognize that incomplete follow-up may result in underreporting of ICA and revascularization. Since cardiac catheterization services and cardiac surgery are centralized to our tertiary-care centre (servicing a population of 1.5–1.8 million), the majority of cardiac events and revascularization procedures would have been performed locally and thus captured in our database. Telephone follow-up in the CTA population was also performed to ensure completeness of data. Though there was no telephone follow-up performed in the SPECT population, this would potentially bias the results in favour of SPECT.

Conclusions

The results of this study demonstrate that the number of downstream ICA after CTA is similar to that of SPECT. Though CTA appears to be a viable non-invasive diagnostic modality, larger cohort studies are required to understand downstream utilization of resources after CTA.

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References


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