Effective dose of prospective ECG-gated 320-row coronary computed tomography angiography in the diagnosis of coronary artery disease

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Coronary artery disease (CAD) is the number one cause of death globally, and it is estimated that 7.3 million people died from CAD in 2008.\(^1\) This number is projected to increase, and CAD will remain the single leading cause of death.\(^2\) The diagnosis of this disease is not always clear, and a large number of patients present inconclusive biomarker and ECG changes.\(^3\) Safe, accurate and early diagnosis is critical to identify or exclude CAD.\(^2\)

Coronary computed tomography (CT) angiography is a non-invasive and highly accurate imaging modality for diagnosing CAD.\(^2\,^5\,^6\,^13\) However, the high effective dose of radiation and subsequent adverse events are concerning.\(^2\,^4\) A number of dose reduction strategies have been implemented, including prospective ECG-gating, low kV and high-pitch settings, and the use of a multi-slice dual source scanner.\(^4\) The latest generation of 320-row coronary CT angiography (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) was introduced to John Hunter Hospital (JHH) in April 2010. Since then, it has been used as the main scanner for CT coronary angiograms. We evaluated the radiation dose delivered during coronary CT angiographies performed in JHH in the present study and compared our findings to comparable published data.

The objectives of the study were as follows:

1. Examine the radiation dose delivered during coronary CT angiography overall and between groups according to heart rate.
2. Compare our radiation doses to the findings from other centres (from published studies and meta-analyses)
3. Formulate the reasons for these dosages and examine how we can modify our practice to further minimise radiation exposure.
Methods and materials

Study design

This is retrospective review of coronary CT angiographies in a single-institution for the assessment of coronary artery stenosis in high-risk patients between July 2011 and July 2014. A Radiology Information System (RIS) and Picture Archiving and Communication System (PACS) were used for data collection and these were carefully analyzed. The regional ethics committee approved the study protocol.

Study group

The study group consisted of any patients with clinically suspected coronary artery disease who had the coronary CT angiography in the JHH. Patients with arrhythmia or known coronary artery disease (including percutaneous coronary intervention or coronary artery bypass surgery) were included. Patients with impaired renal function (serum creatinine >110 µmol/L), contrast allergy or pregnancy were excluded.

Coronary CT angiography Image Acquisition

Each patient received organic nitrate vasodilator glyceryl trinitrate (Nitrolingual Pumpspray, Sanofi- Aventis, Sydney, Australia) one or two sublingual spray (equivalent to 400 to 800 microgram) 5 minutes prior to start scan to assist interpretation by dilating coronary artery. In addition, majority patients received cardioselective beta1-blocker metoprolol oral 50 to 100 mg and or intravenous 5 to 10mg prior to the CT scan in order to achieve heart rate #65 beats per minute (bpm) 1 hour before data acquisition. This allows long rest period of the coronary arteries so that images can be acquired within a single heartbeat.

Imaging was performed with a snapshot (no table movement, pitch of 0) whole heart-scan on a 320- row CT with 0.5mm detector elements, 350 milliseconds of gantry rotation time, and up to 16cm of craniocaudal coverage. Prospective CT angiography was performed from 70% to 80% and 30% to 80%of the RR interval in patients with heart rates of #65 and >65 beats per minute (bpm), respectively. Scanning settings of 100 to 135 kV were used. The patients’ weight and height were not measured.

Every patient had a breath hold practice to adjust scanner settings to individual patients. Nonionic, water-soluble intravenous contrast ULTRAVIST®370 (iopromide) 50mL was then injected with normal saline flush of 50mL.
Dose-length product measurements were displayed after each scan on the scanner’s console. Radiation exposure for whole-heart CT angiography was quantified with a dose-length product conversion factor of 0.014 mSv/mGy x cm.

**Variable definitions**

It has been previously found that heart rate influences duration of CT and therefore higher heart rate can lead to increased radiation dose. We have categorised JHH patients based on heart rate during CT (Low #65, High >65, Bypass) for descriptive purposes. Due to the lack of data on heart rate groups in other published studies (N, std deviation), instead of grouping patients based on heart rate during CT, heart rate was included in regression modelling as a continuous measure (mean, std deviation).

**Statistical analysis**

Descriptive statistics are presented by counts and percentages for categorical variables and means (standard deviation) for continuous variables. Comparison of continuous variables was performed using ANOVA or Kruskal-Wallis (3 groups) and using Chi2 test for categorical variables.

Random effect meta-analysis of previously published results and including our outcomes was performed using Metan statistical coding in Stata to compare radiation doses. Random-effects analysis allows for the true effect size of the effective radiation dose to vary between studies, incorporates an estimate of between-study variation (heterogeneity) in the weighting and gives relatively greater weight to smaller studies than fixed-effect analyses. Meta analysis was performed:

- On all published studies
- Stratified by slice number
- Limit to 320 slice studies only

Meta regression was performed using linear mixed models implemented and restricted maximum likelihood estimation (reml) to examine association between slice number and radiation dose. 3 models were performed:

- A null (intercept only) model to examine the mean outcome effect across studies and between-studies variation for mean effective dose
- Slice number added to the model to look at its association with effective dose, and whether its addition explains (reduces) some of the between-study variance
- Adjust the model for heart rate (as a continuous mean reported from each study) and determine whether it is association with effective dose, and whether its addition explains some of the between-study variance
SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata 13.0 (StataCorp LP, College Station, Texas USA) was used to for analyses.
Results

Description of JHH data

Data were collected from 385 patients who underwent coronary CT angiography at JHH between 6/7/2011 and 30/7/2014; the demographics and scan characteristics are shown in Table 1.

Meta-analysis

A total of 24 studies were found that described coronary CT angiography outcomes using 32-, 64- or 320-slice scanners; the JHH data were added to this set of studies. Table 2 shows the study characteristics.

Several papers reported results categorised by heart rate (Table 3). However, the studies did not report the number of patients in each heart rate group and as such, the standard error could not be calculated.

The meta-analysis was performed to examine the mean effective radiation dose. Only studies with a mean and standard error for the effective dose were included in the meta-analysis; a total of 19 studies were included. Figure 1a includes all studies stratified by slice number, and figure 1b includes only the studies that used 320 slices.

The pooled mean effective dose estimate was 5.37 mSv (95% CI 4.75-6 mSv) across all studies. In the 32-slice studies, the pooled estimated mean effective dose was 2.54 mSv (95% CI 2.27-2.81 mSv); in the 64-slice studies, the pooled estimated mean effective dose was 3.01 mSv (95% CI 2.08-3.94 mSv); and in the 320-slice studies, the pooled estimated mean effective dose was 9.98 mSv (95% CI 7.32-12.64 mSv). The effective dose mean for JHH (8.5) falls within the 95% CI of the overall effective dose estimate, indicating that it is not significantly different from the results of other published studies.

Heterogeneity statistics (I²), which describe the extent to which the effective dose estimates varied between studies, are displayed; the I² statistic is the percentage of between-study heterogeneity that can be attributed to variability in the true treatment effect rather than sampling variation (chance). Among all slice number groups, there is a significant between-study heterogeneity (93-99.5%).
Meta regression

Meta regression was performed to examine the association between slice number and effective radiation dose and the heterogeneity of the effective dose estimates between studies. Three models were created (Table 4). 1) A null model with no covariates was created to examine the effective dose averaged across all studies and the between-study variation in the effective dose. 2) A model that included slice number (continuous) and 3) a model that included both slice number and heart rate (continuous) were created to examine whether the covariates were significantly associated with the outcome and the between-study variance. Estimates of the intercept represent the mean effective dose; in models 2 and 3, the estimates for slice and heart rate represent the increase in effective dose for every 1 point increase in slice number or heart rate.

Model 1 reveals that the estimated mean effective radiation dose was 5.82 mSv across all studies, which was significantly different from the null value of 0 (p<0.0001); this estimate varies slightly from the pooled estimate of 5.37 in the forest plot due to differences in the pooling methods. The estimated variance parameter differed significantly from zero (deviance statistic, p<0.001), indicating a significant between-study variation in the effective dose.

The slice number was found to be significantly associated with the effective dose in model 2, and its addition to the model reduced (explained) some of the between-study variation.

Both slice number and heart rate were significantly associated with the effective dose (model 3), and the addition of heart rate further explained some of the between-study variation.

Figure 2 plots the predicted effective dose (calculated from model 3) against the slice number with a regression line (95% CI). The results from JHH are shown in red with a 95% CI.

As shown in the meta-analysis, the effective dose estimate for JHH falls within the 95% CI for the regression line, indicating that it is not significantly different from the results of other studies.
Table 1: Table 1. Descriptive statistics by heart rate group

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Table 2: Table 2. Summary statistics of studies included in meta-analysis

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Table 3: Summary statistics of meta-analysis by heart rate

<table>
  <tr>
    <th>Paper</th>
    <th>Author</th>
    <th>Heart rate group</th>
    <th>Mean Effective Dose (SE)</th>
  </tr>
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    <td>8</td>
    <td>Dewey</td>
    <td>Low Heart rate</td>
    <td>3.9 (.)</td>
  </tr>
  <tr>
    <td>Dewey</td>
    <td>High Heart rate</td>
    <td>12.3 (.)</td>
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  <tr>
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    <td>6 (.)</td>
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  <tr>
    <td>De Graaf</td>
    <td>High Heart rate</td>
    <td>3.9 (.)</td>
  </tr>
  <tr>
    <td>15</td>
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    <td>Low Heart rate</td>
    <td>9.6 (.)</td>
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    <td>High Heart rate</td>
    <td>14.2 (.)</td>
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    <td>22.6 (.)</td>
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  <tr>
    <td>23</td>
    <td>VanVelzen</td>
    <td>Low Heart rate</td>
    <td>3.6 (.)</td>
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    <td>Low Heart rate</td>
    <td>7.1 (.)</td>
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    <td>20.7 (.)</td>
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  <tr>
    <td>JHH</td>
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  </tr>
  <tr>
    <td>JHH</td>
    <td>Bypass</td>
    <td>29 (0.75)</td>
  </tr>
</table>
Fig. 1: Fig 1a. Forest plot displaying a random-effect meta-analysis of the effective dose for CT angiography, by slice number 2-5, 8, 9, 11, 15-20, 22-26

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**Fig. 2:** Figure 1b. Forest plot displaying a random-effect meta-analysis of the effective dose for 320-slice CT angiography2-5,8,9,11

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Fig. 3: Figure 2. Predicted effective dose and slice number from meta regression

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Conclusion

Discussion

This study reveals significant variation in the effective radiation dose of 320-row coronary CT angiography between groups according to heart rate. The high heart rate and bypass groups received much higher radiation dosages compared to the low heart rate patients. This result occurred because a higher heart rate caused the scanner to need to acquire data over multiple cardiac cycles to increase the temporal resolution, which ultimately increases the exposure time.\textsuperscript{5} In this study, image acquisition was manually adjusted to each individual patient’s heart rate while the patient practiced breath-holding. For heart rates of \#65 and >65 bpm, one- and two-heart-beat acquisition modes were used, respectively, to improve image quality. The overall mean effective radiation dose at JHH is not significantly different than those reported in other studies. It is also important to note that patients with arrhythmia or known coronary artery disease (including percutaneous coronary intervention or coronary artery bypass surgery) were included in this study.

Using 320-row coronary CT angiography, the entire heart can be imaged in three dimensions in a single gantry rotation. This feature can reduce the radiation exposure by 4- to 5-fold because it avoids the over-scanning that is associated with helical scanning techniques.\textsuperscript{5,7} In addition, 320-row coronary CT angiography offers the advantage of imaging with minimal motion artefacts, such as step artefacts and blurring artefacts, which can degrade the diagnostic value.\textsuperscript{3,27} In this study, fewer artefacts were noted in the low heart rate group, further highlighting the importance of improved heart rate control, as this strategy will minimise both blurring artefacts and the radiation dose.\textsuperscript{26} The image quality is further influenced by the contrast filling and cardiac rhythm.

320-Row coronary CT angiography is non-invasive and safe. However, a 45-year-old female experienced skin rash without bronchospasm or laryngeal oedema soon after the contrast media, iopromide, was injected. The patient was non-diabetic, had no known drug allergies and normal renal function. Iopromide is commonly used as a non-ionic monomer contrast agent for coronary CT angiography. In general, contrast media are safe, but adverse reactions can occur.\textsuperscript{27} Hypersensitive reactions may vary from mild to severe. Mild contrast media reactions to non-ionic contrast injections usually occur in less than 3% of patients, and severe reactions usually occur less than 0.04% of patients.\textsuperscript{27} Mortality due to contrast media reactions is extremely rare, but the rate is significantly higher in the elderly.\textsuperscript{28,29} Every patient must be screened for risk factors. The most important risk factor is a previous reaction to contrast media, as it indicates a 20% to 60% absolute chance of a reaction following exposure.\textsuperscript{27} Current medications, a history of asthma and multiple allergies must be carefully evaluated.
With the administration of contrast media, metformin use can cause severe renal failure and lactic acidosis, whereas beta-blockers are associated with hypersensitivity and the worsening of bronchospasms. If a reaction occurs, infusion of the contrast media must be ceased and treated immediately as an anaphylactic reaction. Appendix A demonstrates information for the contrast medium and a questionnaire.

Some limitations of the study should be noted. First, body mass index (BMI) and thoracic anatomy should be considered when determining tube voltage and current settings. In this study, a scanning setting of 100 to 135 kV and tube current of 400 to 580 mA were selected depending on the patient’s body habitus without actually measuring the BMI. Using an appropriately low kV in prospective ECG-gating will result in a 46% radiation dose reduction without compromising the image quality. Second, publication bias exists, as non-English publications were not considered. Third, coronary CT angiography is only a diagnostic; therefore, patients with significant coronary artery stenosis will subsequently require invasive coronary angiographies with additional radiation exposure. This issue suggests the importance of appropriate patient selection for CT angiography among patients with a low to intermediate risk of disease.

Conclusions

This retrospective review and meta-analysis suggest that the effective dose mean for JHH is not significantly different from those reported in other published studies. The heart rate should be controlled to <65 bpm to reduce the radiation dose and improve the diagnostic image quality.
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