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5

6 Introduction

7 Attenuation correction (AC) has become necessary in myocardial perfusion imaging
8 (MPI) due to the likelihood of photon attenuation artefacts. In addition to a general
9 reduction of photon counts in larger patients, localised photon attenuation artefacts
10 typically caused by diaphragmatic attenuation in larger males and breast attenuation
11 in larger females (1,2) can cause difficulties in interpretation. Misinterpretation could
12 lead to unnecessary invasive intervention, such as coronary angiography. This type of
13 error is clinically unacceptable, and a high-quality attenuation map is recommended
14 to correct for these patient induced artefacts (3). For these reasons AC is
15 recommended by the American Society of Nuclear Cardiology and Society of Nuclear
16 Medicine for MPI studies (4).

17 AC was initially performed using radionuclide based transmission images but has
18 been superseded by an x-ray computed tomography (CT) based technique (5-7)
19 In comparison to a radioactive line source, CT based AC has improved the quality of
20 the attenuation map due to better spatial resolution, increased photon flux and no
21 cross-talk from different radionuclide gamma ray energies. As a result MPI studies
22 have seen improvements in diagnostic accuracy (8,9).

23 While the usefulness of CT based AC is clear there is controversy regarding what
24 must be done about the incidentally produced low-resolution CT images that are the
25 basis of AC.

26 In the United Kingdom (UK), regulations dictate that a clinical evaluation and record
27 must be made for every exposure (10). The implication here is that all image
28 information should be reviewed, regardless of the reason for exposure (i.e. AC and
29 not a diagnostic quality scan). However, the typically low quality of images produced
30 for AC in single photon emission computed tomography/computed tomography
31 (SPECT/CT) means that it is not clear whether this could be counterproductive. To
32 further complicate this, the diagnostic quality of these images is also liable to
33 significant variation due to the diversity of CT parameters used for an AC acquisition
34 in different SPECT/CT systems. Despite variation in the acquisition, the reliability of
35 attenuation maps provided by CT units has been found to be independent of both
36 tube charge (mAs) (11) and tube rotation speed (12). Furthermore a static phantom
37 study of the low-resolution CT images produced by a single SPECT/CT system for AC
38 has reported that mAs had no impact on an observer's ability to detect certain
39 simulated lesions (13).

40 Some retrospective clinical work has been done to evaluate the diagnostic suitability
41 of these low-resolution images; Goetze et al (14) studied 200 consecutive patients
42 undergoing attenuation corrected MPI using CT based AC in a single SPECT/CT
43 system. The review of these coincidentally acquired low-resolution images revealed
44 234 extracardiac abnormalities in 119 patients; 15 previously undiscovered incidental
45 findings were categorized as having major significance, requiring either further
46 testing or follow-up. An expert in CT and a resident in nuclear medicine with no

47 formal CT training completed this retrospective review and the results described the
48 consensus opinion. Based on the consensus opinion the authors recommended
49 routine assessment of these low-resolution images. However, no receiver operating
50 characteristic (ROC) study was completed and their study was confined to a solitary
51 SPECT/CT system while in practice there is considerable variation in acquisition
52 parameters and other device characteristics between SPECT/CT systems in clinical
53 use. The current study investigates the impact of the CT acquisition parameters used
54 in five SPECT/CT systems in the UK.

55

56 **Materials and Methods**

57 **Image Acquisition**

58 Since it would not be desirable from ethical and practical considerations to image
59 enough patients in all five modalities to generate sufficient numbers of normal and
60 abnormal cases for the observer study, a phantom study was indicated. Phantom
61 simulation allows the production of reliable system-matched images without
62 concerns over radiation dose.

63 Spherical simulated lesions with diameters 3, 5, 8, 10 and 12mm, and densities -800,
64 -630 and +100 Hounsfield Units (HU), for a total of 15 inserted lesions (some
65 diameter-density combinations were repeated) which were manually inserted in 17
66 trans-axial slices in an anthropomorphic chest phantom (*Lungman N1 Multipurpose
67 Chest Phantom, Kyoto Kagaku Company Ltd, Japan*) representing a 70Kg male. The
68 lesions were composed of urethane (-800 and -630HU) and a combination of
69 polyurethane, hydroxyapatite and a urethane resin (+100HU). This resulted in 17

70 abnormal image slices, each containing 1-3 simulated pulmonary lesions, and 9
71 normal slices, i.e., containing no lesions. The phantom was scanned on a dedicated
72 diagnostic quality multi-detector CT (MDCT) scanner, not to be confused with CT
73 units in the SPECT/CT systems, which were the subject of the comparison study. The
74 MDCT images provided a lesion reference map that would act as the truth (gold-
75 standard) for the observer performance study. The high-resolution MDCT scan was
76 repeated at the end of the SPECT/CT imaging, described next, to ensure that lesion
77 positions had not changed.

78 All images for the observer study were produced from a single CT acquisition of the
79 phantom from each SPECT/CT system using site-specific CT acquisition protocols,
80 Table 1, appropriate to a 70Kg male. The variation in CT acquisition parameters and
81 estimated CT Dose Index (CTDI) listed in this Table is representative of general
82 practice in the UK. The variation in slice thicknesses gave rise to a differing number of
83 axial CT slices but each acquisition covered the full length of the phantom. Four
84 SPECT/CT systems (labelled 1-4) used low-resolution CT systems from the same
85 manufacturer, and the fifth (labelled 5) used a CT system capable of producing
86 diagnostic quality images from a different manufacturer, which was used as a backup
87 to the dedicated diagnostic CT system in that imaging facility.

88 Figure 1, which shows two representative slices imaged using each SPECT/CT system,
89 is arranged in 5 rows (labelled with numbers 1-5 corresponding to the 5 SPECT/CT
90 systems) and two columns: the first labelled (a) corresponds to the abnormal slice
91 (the arrow points to the location of the simulated lesion) and the second labelled (b)
92 corresponds to the normal slice. Since the slices were not viewed in three-
93 dimensional volumetric mode, care had to be exercised in choosing the central

94 locations of the chosen slices so that sets of five “matched” slices, for example, those
95 corresponding to each column in Figure 1, corresponded to the same physical region
96 of the phantom. For normal slices this was achieved using anatomical landmarks
97 (simulated major vessels and bony structures) visible on the high-resolution MDCT
98 images. For abnormal slices this was achieved by selecting that slice that maximized
99 the visual contrast of the contained lesion.

100

101 **Observer Performance Study**

102 Each CT acquisition produced 26 image slices for the observer performance study.
103 Twenty-one professionals working in nuclear medicine (0-4 years CT experience,
104 mean 1.2 ± 1.2) each completed the study in a single session lasting approximately 90
105 minutes. No time restriction was enforced. All selected Images, 26 from each of the 5
106 SPECT/CT systems were pooled together and displayed in a different randomised
107 order for each observer. The observer was unaware of the SPECT/CT system used to
108 generate each image. Observers were informed they would be interpreting 17
109 abnormal image slices, each containing 1-3 simulated pulmonary lesions, and 9
110 normal slices, imaged in five modalities. They were required to localise all suspicious
111 areas precisely using mouse clicks. Additionally, an individual confidence score
112 rendered on a 10-point integer (1-10) rating scale, was required for each localisation
113 (mark); this was implemented using a slider bar. Image evaluations were conducted
114 using ROCView (15) (*Bury St Edmunds, UK, www.rocview.net*) on identical monitors
115 (*iiyama ProLite B2206WS 22 inch widescreen LCD, iiyama, Netherlands*) (1680x1050
116 pixels, 1.8 megapixel resolution), satisfying the standards set by The Royal College of
117 Radiologists (16). Observations were completed in low ambient light environments.

118 Lesion visibility was maximised using a lung window setting (width 1500, level -500)
119 which was held fixed for all observers.

120

121 Each localisation (mark) was classified (scored) as lesion localisation (LL) or non-
122 lesion localisation (NL) using a 20-pixel radial diameter acceptance radius (AR)
123 centred on each lesion. To test for effects of varying the acceptance radius, the data
124 was also analysed using a 40-pixel acceptance radius. The analysis was repeated for
125 two subgroupings of readers according to experience: 7 readers with no CT
126 experience and 14 readers with CT experience.

127

128 **Statistical Analysis**

129 Multi-reader multi-case (MRMC) FROC ratings corresponding to 2730 (26 cases X 21
130 observers X 5 SPECT/CT systems) individual slice observations were analysed using
131 the jackknife alternative FROC (JAFROC) method (17) (*JAFROC 4.2*,
132 www.devchakraborty.com/downloads). The outcome analysed was the unweighted
133 JAFROC figure of merit (FOM), which is the empirical probability that a lesion is rated
134 higher than any mark on a normal case (equal weighting was employed). The
135 software also outputs the numbers of LL marks per slice and the average numbers of
136 NL marks per normal slice, and the corresponding number per abnormal slice.
137 The DLL module used for the significance testing was developed at the University of
138 Iowa (18-24). The relevant statistics provided by the software are the F-statistic and
139 p-value for testing the null hypothesis that all SPECT/CT systems have identical
140 performance, the individual and observer averaged FOMs for each SPECT/CT system,
141 the FOM differences between pairs of SPECT/CT systems, and 95% confidence

142 intervals for the FOMs and the paired differences. Since the results are specific to the
143 particular phantom and slices used in the study, random-reader fixed-case results
144 reported by the software are used. Analyses using the software were conducted
145 separately for the four subsamples corresponding to the two values of acceptance
146 radius (AR) and the two levels of CT experience. Since cases are treated as fixed, the
147 observer FOMs, averaged across the five SPECT/CT systems are independent.
148 Therefore we apply a two-independent-group t-test to the observer averaged FOMs
149 (where CT experience is the grouping variable), providing a confidence interval. If the
150 global test is significant, then we follow it by individual within-system confidence
151 intervals. Type I error is controlled as follows. Consider the family of tests consisting
152 of the five global tests: four tests for identical system performance and one test of
153 identical experience performance. For this family the maximum type I error rate
154 (probability that we will incorrectly conclude that there are any differences for any of
155 the five groups) is limited to 0.05 by performing each of the five tests at the
156 Bonferroni corrected level of $\alpha = 0.01$. Follow-up 95% confidence intervals and
157 corresponding hypotheses tests ($\alpha = 0.05$) for pair-wise differences are reported
158 only if the corresponding global test is significant; in this way, for a particular global
159 test the overall type I error for follow-up tests (i.e., the probability that we will
160 incorrectly observe any differences) is limited to .05 if there are no real differences.
161 Thus, in order for a statistically significant difference to be declared, the p-value of
162 the overall F-test had to be smaller than 0.01 and the 95% confidence interval for the
163 paired difference between FOMs had to exclude zero.

164

165 **Plotting free-response data**

166 Single rating per image ROC data is usefully visualized via the receiver operating
167 characteristic (ROC) curve. Free-response data, consisting of mark-rating pairs, can be
168 visualized in 3 ways. (1) The highest rating of all marks on a slice (or zero if the slice
169 has no marks) is the highest rating inferred ROC rating of the slice; this can be used to
170 construct inferred ROC curves (true positive fraction, TPF, vs. false positive fraction,
171 FPF). (2) The FROC (free-response ROC) is the plot of lesion localization fraction (LLF =
172 fraction of lesions correctly localized) vs. non-lesion localization fraction (NLF =
173 number of non-lesions divided by the total number of slices). (3) The AFROC
174 (alternative free-response ROC) is the plot of LLF vs. FPF: a linear interpolation from
175 the uppermost operating point to (1,1) is included in the area under the AFROC,
176 which is the JAFROC figure of merit.

177 Empirical ROC/FROC/AFROC curves were produced for each SPECT/CT system. For
178 the AFROC, linear interpolation was used to estimate the lesion localization fraction
179 (LLF) for all observers at 200 abscissa values between operating points (0.005
180 increments between 0 and 1) and these were averaged to yield the reader-averaged
181 plot.

182

183 Results

184 Table 2 summarizes the results of the four analyses conducted (for AR = 20, 40, CT
185 experienced and no CT experience): it lists the F statistic, and in parenthesis the
186 numerator and denominator degrees of freedom, the P-value, the average number of
187 NL marks per normal slice, the corresponding number per abnormal slice, and the
188 average number of LL marks per abnormal slice. For 20-pixel acceptance radius and

189 all 21 readers, Figure 2a displays the JAFROC FOMs and 95% confidence intervals for
190 the five SPECT/CT systems; the FOM values were 0.602, 0.639, 0.372, 0.475 and
191 0.719 respectively. Figure 2 (a) shows that system 3 had the lowest FOM, while
192 system 5 had the highest, 1 and 2 were similar, and slightly below 5, while 4 was
193 intermediate between 3 and 5. Differences between pairs of SPECT/CT system and
194 corresponding confidence intervals are shown in Figure 2b. A statistically significant
195 difference in FOMs (confidence interval not including zero) was found between all
196 but one pair of SPECT/CT systems (the 1-2 pairing difference was not significant –
197 these systems only differed in mAs values, Table 1). SPECT/CT system 5 was
198 significantly superior to all other SPECT/CT systems. The significance of differences in
199 SPECT/CT system pairings were unchanged for the other three analyses (AR = 40, CT
200 experienced, no CT experience) with one difference: the SPECT systems 1 vs. 2
201 difference became significant (with 2 superior) for AR = 20 for the CT experienced
202 readers – i.e., the higher mAs system was significantly superior for the experienced
203 readers provided the tighter acceptance radius criterion was adopted.
204 Figure 3 shows reader averaged inferred ROC, FROC and AFROC curves for AR = 20
205 and all 21 readers. The AFROC/FROC curves for AR = 40 are visually identical to those
206 shown in Figure 3; the small increments in FOM are not visually apparent. Since
207 localization specific scoring is not performed in ROC analysis, the ROC curves are
208 independent of AR. Figure 4 compares the reader averaged FOMs of the CT
209 experienced, n = 14; and no CT experience, n = 7. Despite a trend towards higher
210 FOMs for the experienced group (modality averaged value = 0.596 for experienced
211 group vs. 0.492 for the inexperienced group), the Welch's 2-sample t-test of the
212 modality-averaged JAFROC FOMs between the two experience based reader groups

213 revealed no significant difference in lesion detection performance on the basis of CT
214 experience ($p = 0.0539$, subgroup difference 0.105 (95% CI -0.002, 0.211)).

215

216 Discussion

217 This study evaluated lesion detectability in the low-resolution CT images acquired for
218 attenuation correction as part of the SPECT/CT myocardial perfusion imaging
219 technique. The diagnostic value of these images has been in question, but the work
220 of Goetze et al (14) has suggested that there is value in reporting interpretations
221 from these images. Legislative pressures in the UK also require a formal record of
222 each exposure to be created.

223 The statistically significant differences observed in this study, which were especially
224 large for SPECT/CT system 5 compared to the others, suggest that there may be some
225 clinical implications of the differences in image acquisition parameters between
226 clinical centres. We believe this is the first work to assess the influence of the CT
227 protocol on the diagnostic potential of the attenuation corrected images in patients
228 undergoing myocardial perfusion imaging.

229

230 Previous work (13) with 20 readers on the detection of simulated lesions on CT
231 images acquired for AC using a free-response study was unable to demonstrate
232 statistically different performance when changing mAs over the range 15.8 to 39.5.

233 The current work was likewise unable to detect a mAs effect if all observers were
234 included ($n=21$; AR = 20 and 40 pixels). However, when we restricted to CT
235 experienced observers ($n=14$) and a tight acceptance radius (AR = 20 pixels) the mAs

236 effect (SPECT systems 1 vs. 2) became significant. The ability to demonstrated
237 significance is likely due to two factors: (i) using the more lax acceptance radius (AR =
238 40) is expected to confuse perceptual NLs (incorrect decisions) as LLs (scored correct
239 decisions) (25), and (ii) using experienced observers is expected to reduce inter-
240 reader variability. Both of these effects are expected to increase statistical power.

241

242 From examination of Figure 2 (b), and focusing on the differences with the largest
243 magnitudes, it appears that the axial (z-axis) resolution (i.e., reconstructed slice
244 thickness) and matrix size appear to be the main factor in determining lesion
245 detection performance, with smaller slice thickness and larger matrix sizes
246 contributing to higher performance. The comparatively higher performance of
247 system 2 (6.1 mm thick slices) relative to system 3 (10mm thick slice) is consistent
248 with the slice thickness effect, as is the superiority of system 5 (5 mm thick slices) to
249 all other systems. The superiority of system 4 to 3 is attributable to the larger matrix
250 size of the former. SPECT/CT system 5, the only system with diagnostic capability,
251 showed the highest observer performance, being statistically better than all other
252 systems. System 5 uses a lower kilovolt potential and a smaller pixel size to offer
253 improved image contrast and spatial resolution respectively. The reconstructed slice
254 thickness is also smaller, thus providing improved axial resolution.

255 Initially we had concerns that a larger reconstructed slice thickness may favour lesion
256 detection, when using single axial images vs. three-dimensional display, due to less
257 noise being present in the image. However lesion detection improved as the
258 reconstructed slice thickness decreased, suggesting that the partial volume effect has
259 a greater impact on lesion detection than image noise.

260 While lesion detection performance for the CT experienced group was somewhat
261 higher than for the inexperienced group, Figure 4, the difference was not statistically
262 significant. However, this subgroup analysis may have relevance to the nuclear
263 medicine community, where CT interpretation skills can vary broadly due to the
264 training pathway of those reporting myocardial perfusion imaging studies (i.e.
265 radiologist vs. nuclear medicine physician). It has been suggested that further
266 training might be required for clinicians with less experience in CT to recognise extra-
267 cardiac findings and establish the need for follow-up (26). More specifically, it has
268 been recommended (27) that nuclear medicine physicians without CT training should
269 report only the functional data (SPECT) with radiologists involved to report the
270 anatomical data (CT), therefore providing a collaborative report.

271

272 This laboratory study reflects the variation in CT protocols used for AC in the UK.
273 However, limitations are evident in this type of phantom study. Respiratory motion
274 was not simulated and this is likely to have effect in a patient population. In this
275 study, tube rotation times ranged from 1.5 seconds (treatment 5) to 23.1 and 30
276 seconds (treatments 1-4) which could allow 4-5 normal breathing cycles to occur,
277 thus allowing greater potential for respiratory motion artefacts (28). Respiratory
278 motion artefacts are evident with slow and fast tube rotation speeds, with greater
279 impact on slow rotations (29).

280

281 Conclusion

282 Protocol variations in operation for CT based AC have a significant impact on lesion
283 detection performance. The results imply that z-axis resolution and matrix size had
284 the greatest impact on lesion detection, with a weaker but detectable dependence
285 on the mAs product.

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290

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293 DLL module used in the ANOVA analysis at the University of Iowa by Professor Kevin
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298 analysis.

299

300

301

302 Figure Captions

303 Figure 1: An abnormal slice (left column, labelled a) containing a 12mm and -630 HU
304 simulated lesion (arrowed), and a normal slice (right column, labelled b) for each of
305 the five SPECT/CT systems (numbered 1 - 5) used in this study.

306

307 Figure 2a: JAFROC figures-of-merit (FOM) and 95% confidence intervals for the 5
308 SPECT/CT systems (AR = 20).

309

310 Figure 2b: FOM difference (AR = 20) for all SPECT/CT system pairings (labelled on the
311 x-axis; e.g., 1 – 2 means FOM for system 1 minus that for system 2) and 95%
312 confidence intervals. Confidence intervals that do not include zero demonstrate a
313 significant difference between the corresponding treatments.

314

315 Figure 3: Empirical reader averaged ROC, FROC and AFROC curves for all SPECT/CT
316 systems using an acceptance radius of 20-pixels.

317

318 Figure 4: Illustrating the effect of CT experience. Shown are reader averaged JAFROC
319 figures-of-merit and 95% confidence intervals. CT experience: 14 readers; no-CT
320 experience: 7 readers.

321

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