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Comparison of simultaneous and sequential SPECT imaging for discrimination tasks in assessment of cardiac defects

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Abstract

Simultaneous rest perfusion/fatty-acid metabolism studies have the potential to replace sequential rest/stress perfusion studies for the assessment of cardiac function. Simultaneous acquisition has the benefits of increased signal and lack of need for patient stress, but is complicated by cross-talk between the two radionuclide signals. We consider a simultaneous rest ^{99m}Tc -sestamibi/ ^{123}I -BMIPP imaging protocol in place of the commonly-used sequential rest/stress ^{99m}Tc -sestamibi protocol. The theoretical precision with which the severity of a cardiac defect and the transmural extent of infarct can be measured is computed for simultaneous and sequential SPECT imaging, and their performance is compared for discriminating (1) degrees of defect severity, and (2) sub-endocardial from transmural defects. We consider cardiac infarcts, for which reduced perfusion and metabolism are observed. From an information perspective, simultaneous imaging is found to yield comparable or improved performance compared with sequential imaging for discriminating both severity of defect and transmural extent of infarct, for three defects of differing location and size.

Keywords

Ideal estimation; simultaneous SPECT imaging; cardiac defects

1. Introduction

Myocardial perfusion imaging is a widely-used technique for assessing cardiac function and viability. Although not employed in primary emergency care, it is often used in stabilized patients in the days following a cardiac event, and as an assessment of function for referring general practitioners for patients presenting with early cardiac symptoms. In stable patients, nuclear imaging may be used to determine extent of damage once angiography has identified stenoses, or to detect coronary artery disease (CAD). To detect perfusion defects, rest and stress perfusion imaging is required to differentiate normal, ischemic and infarcted tissue. To differentiate viable from scarred tissue, both metabolism and perfusion are required to understand the functional state of myocardium. Hence, two pieces of information are required in many routine cardiac studies. For example, rest/stress and rest/redistribution protocols are able to identify reversible and fixed defects, and perfusion/ metabolism protocols identify matched and mis-matched regions. While a normal stress scan automatically indicates a normal rest scan, rest scans are usually undertaken first to prevent the possibility of a stress-induced defect contaminating the rest image. In this study, we consider necrotic (non-viable) regions of the myocardium, which display both perfusion and metabolism defects.

Metabolism of fatty-acids is the normal route for energy generation in the myocardium. After a cardiac event, the affected region's myocytes downregulate fatty-acid metabolism and upregulate glucose metabolism. Fatty-acid radiotracers have been shown to display regions of ischemia after blood flow has been restored (Kumita et al., 2000). It is therefore useful as a marker of ischemic memory. In our study, we will consider fatty-acid tracers injected while ischemia remains and is thus also visible on the stress perfusion scan.

Simultaneous imaging of two radiotracers has the advantages of increased signal for the same total imaging time, identical patient physiological state, registered images and the potential for earlier diagnosis. In addition, if patient stress is not required, there is reduced potential for patient discomfort or undesirable medical side-effects. The major disadvantage of simultaneous dual-isotope imaging is the potential for signal confusion, due to cross-talk of photons between the two photopeaks. The signals are differentiated on the basis of energy, however closely-spaced photopeaks and photon downscatter make perfect signal separation impossible.

Sequential rest and stress imaging with ^{99m}Tc -sestamibi is either performed on the same day or over a two-day protocol. It requires multiple use of the scanner and the need to stress a patient who has potentially suppressed cardiac function. Simultaneous rest ^{99m}Tc -sestamibi perfusion and rest ^{123}I -BMIPP fatty-acid metabolism can provide similar information to rest/stress perfusion imaging without the need for patient stress.

Simultaneous dual-isotope imaging has been used for a number of applications in SPECT imaging, including neurodegenerative disorders (El Fakhri, Habert, Maksud, Kas, Malek, Kijewski and Lacomblez, 2006; Ma et al., 2009) and cardiac imaging (Fukuchi et al., 2000; Slart et al., 2006; Kiat et al., 1994; Lowe et al., 1993). There was interest in the 1990s in simultaneous dual-isotope $^{201}\text{Tl}/^{99m}\text{Tc}$ myocardial perfusion imaging, including work to correct for cross-talk (Moore et al., 1995), phantom studies to determine optimal imaging protocols (Lowe et al., 1993), and patient feasibility studies (Nakamura et al., 1999). Nakamura et al. (1999) found good agreement between simultaneous $^{201}\text{Tl}/^{99m}\text{Tc}$ imaging and angiography studies for detecting CAD in 81 patients. He et al. (2008) have recently optimized $^{201}\text{Tl}/^{99m}\text{Tc}$ injected activity using a task-based method based on defect detectability. There has also been considerable interest in dual-isotope $^{99m}\text{Tc}/^{123}\text{I}$ studies due to the favourable imaging characteristics of both isotopes and the availability of both for many applications. The major disadvantage of simultaneous $^{99m}\text{Tc}/^{123}\text{I}$ imaging is the similar energy of the two photopeaks (140 keV and 159 keV, respectively), potentially leading to substantial cross-talk. We studied the performance of simultaneous versus sequential ^{99m}Tc -TRODAT/ ^{123}I -IBZM imaging for discriminating between Parkinson's disease states, concluding that the benefits of simultaneous imaging (increased signal) outweighed the detrimental effect of isotope cross-talk (Trott and El Fakhri, 2008). Kumita et al. (2000) assessed the use of simultaneous gated rest ^{99m}Tc -sestamibi and ^{123}I -BMIPP in 130 patients, demonstrating that viability could be assessed with that combination. Several groups have devised and tested cross-talk correction methods for the $^{99m}\text{Tc}/^{123}\text{I}$ combination (El Fakhri, Sitek, Zimmerman and Ouyang, 2006; Ouyang et al., 2007; Du and Frey, 2009), including our group with cardiac phantoms (Ouyang et al., 2009).

Prognosis for patients is dependent on the extent of scar versus viable myocardium, and the extent of involvement of the three major coronary arteries. Cellular viability is identified by demonstrating metabolic activity. In perfusion studies, where metabolism is not studied, viable myocardium may display normal perfusion at rest, but reduced perfusion during stress. However, some states of chronic hypoperfusion can display resting perfusion defects and contractile dysfunction ("hibernating myocardium"), mimicking the behaviour of scar tissue. Evidence of cellular viability is therefore required to discriminate between these

states. There are several important factors that demonstrate viability and predict functional improvement after surgical revascularization (Chan et al., 2008). Two important factors are:

- Reversible defect - while an area of regional damage may exhibit low contractile reserve and perfusion, metabolism may be preserved and re-perfusion is likely to restore function. This viable tissue is demonstrated by a perfusion-metabolism mismatch in a dual-function nuclear imaging study, in an area of contractile dysfunction, or a stress-induced defect combined with a normal rest study;
- Transmural extent (TME) of infarct - patients with scar tissue that spans the entire myocardial wall and the endocardium have a higher risk of cardiac death than those with sub-endocardial infarcts. The TME stratifies patients into medical and surgical treatment paths, and is inversely correlated with prognosis after revascularization.

The severity of a defect (reduced activity compared with normal) and its transmural extent, are therefore important quantities to estimate, and we consider estimation of these quantities for necrotic (non-viable) defects.

In this study we consider only infarcted regions of the myocardium, where perfusion (and metabolism) defects are observed at rest and stress, and results are consistent with no tissue viability. The defect severity (percentage reduction in activity compared with normal myocardium) is assumed the same between rest and stress, and will be the same for the two rest perfusion studies (sequential and simultaneous), and for stress perfusion and rest metabolism. The actual perfusion and metabolism activity concentrations are not the same due to the differences in injected activities, and BMIPP and sestamibi extraction fractions. We wish to understand whether simultaneous imaging with rest ^{99m}Tc -sestamibi/ ^{123}I -BMIPP can achieve comparable discrimination performance to sequential rest/stress ^{99m}Tc -sestamibi. There are many approaches we may take to determine this: for example, asking physicians to discriminate between disease states from images, or using SUVs to measure regional activity. These methods, although related to tasks performed in the clinic, will provide a subjective measure of discrimination performance (i.e., they are appropriate for their method alone, and may not be generally applicable). As a first step, we wish to determine the discrimination performance *objectively*, by considering the information content of images, and assuming unbiased estimation procedures. If simultaneous imaging yields degraded discrimination performance compared with sequential imaging for unbiased and optimal estimators, it is unlikely that the biased and sub-optimal estimation procedures necessarily employed in the clinic will be able to obtain improved results. Hence, this study is an initial, theoretical step to determining the utility of simultaneous rest ^{99m}Tc -sestamibi/ ^{123}I -BMIPP for cardiac imaging. In addition, it has been previously demonstrated that performance for estimation of object activity and size is correlated to object detection performance (Moore et al., 1995). Also, cardiac defect quantitation is becoming increasingly important for physicians assessing perfusion improvement after surgery.

We compare the ability of sequential and simultaneous cardiac SPECT to discriminate degrees of severity (reduction in activity compared with normal myocardium) and transmural versus sub-endocardial defects, for three necrotic defects of varying locations and sizes, from an information perspective. We calculate the theoretical precision with which the defect severity and transmural extent can be estimated for each of the defects. These values for the optimal precision are then used to generate populations of 5000 subjects, using the known parameter value as the population mean, and the estimation precision as the population variance. Pairwise classification of these subjects into groups (degrees of severity, and transmural versus sub-endocardial defects) is then performed. Area under the receiver operator characteristic (ROC) curve is used as the metric to compare the performance of sequential with simultaneous imaging.

2. Materials and Methods

2.1. Data Generation

Computation of the information content of the images requires generation of SPECT projection data (noise-free values), described by an underlying mathematical model. To produce projections of the myocardium with known defect location, size and severity, we use an analytic model for the heart, convolved with a Monte-Carlo simulated point spread function. To this we add Monte-Carlo simulated projections of the background anatomic structure. We construct a mathematical model for the projections, parameterised by the values we wish to estimate: defect severity, transmural extent etc., and compute the estimation precision from this model data.

2.1.1. Projections—The SPECT projections were created as the summation of high-count, low-noise acquisitions of a torso phantom with cardiac insert omitted, and analytic ray-tracing generated projections of the myocardium. The total projection for a simultaneous acquisition, as a function of the model parameters is given by:

$$\begin{aligned}
 P_{ijkl} = & B_{Tc} \text{pr}(\text{back})_{ijkl,Tc} \\
 & + A_{Tc} \{ \text{pr}[\text{myo}]_{ijk} \\
 & + \alpha \text{pr}[\text{defect}(h, \\
 & d, z_0, \phi)] \} \otimes \text{PSF}_{ijkl,Tc} + B_I \text{pr}(\text{back})_{ijkl,I} + A_I \{ \text{pr}[\text{myo}]_{ijk} + \alpha \text{pr}[\text{defect}(h, \\
 & d, z_0, \phi)] \} \otimes \text{PSF}_{ijkl,I}
 \end{aligned} \tag{1}$$

where (i, j) index projection pixels, (k) indexes projection angle, (l) indexes energy bin, and $\otimes$ denotes convolution with a Monte Carlo simulated point spread function. The myocardial projections, ‘pr(myo)’ are generated by ray-tracing through an analytic myocardium, and refer to normal tissue. A_{Tc} and A_I refer to the normal myocardium activity concentrations, and B_{Tc} and B_I refer to the background activity concentrations (soft tissue). The defect projection, ‘pr[defect]’, is parametrised by defect size and location, and is described in section 2.1.3. Sequential imaging projections omit the iodine terms. Two energy windows were used, each straddling one of the radionuclide photopeaks. We used [129,148] keV and [148,175] keV as the two energy windows, in line with those used for the torso phantom acquisitions (Ouyang et al., 2009). The projections of the background tissue used noise-free acquisitions, scaled to an appropriate count value for a clinical study.

We simulated a 15-minute acquisition for each of the rest and stress studies, and a 30-minute simultaneous acquisition. The simulated injected activities were, rest ^{99m}Tc (296 MBq), stress ^{99m}Tc (814 MBq), rest ^{123}I (148 MBq). Myocardial extraction fractions for sestamibi (5.4%) and BMIPP (1.2%) were taken from Kumita et al. (2000), and resulted in normal myocardial activity concentrations of 30.9, 84.9 and 69.5 kBq/cm³ (sestamibi rest, sestamibi stress and BMIPP rest, respectively) with a myocardium of volume equal to 115 cm³.

2.1.2. Phantom acquisitions—We used high-count acquisitions of an anthropomorphic torso phantom with cardiac insert. Full details of the acquisitions are described in Ouyang et al. (2009). We used a dual-head Siemens e.CAM scanner with low-energy high-resolution (LEHR) collimators. Note that the choice of collimator in this work is important because the point spread functions and sensitivity for ^{99m}Tc and ^{123}I isotopes is different. While a LEHR collimator is clinically used for ^{99m}Tc -sestamibi acquisitions, the iodine peak suffers from point spread function degradation due to septal penetration from high energy photons. A medium energy collimator is more appropriate for ^{123}I acquisitions, but produces lower

spatial resolution images (Dobbelair et al., 1999). Noise-free data were acquired with 114.6 million background ^{123}I counts and 273.4 million background $^{99\text{m}}\text{Tc}$ counts.

The standard clinical protocol was used, with 32 projections per head acquired over 90° with two heads positioned normal to each other (total of 64 projections subtending 180°), yielding 64×64 projections with $6.6 \times 6.6 \text{ mm}^2$ pixels. Data were acquired in four energy windows, of which two are used in this work: 129–148 keV (the $^{99\text{m}}\text{Tc}$ photopeak) and 148–175 keV (the ^{123}I photopeak). These windows were based on a previous optimization for these isotopes (Trott and El Fakhri, 2008). A Data Spectrum anthropomorphic torso phantom with cardiac insert was used for the acquisitions. For our studies, the myocardium was filled with zero activity to allow the addition of an analytic myocardium.

2.1.3. Model of myocardium and defects—The analytic myocardium was modelled as the difference between two concentric half oblate ellipsoids, rotated and translated to match the position and orientation of the myocardial insert in the torso phantom. This model was convolved with Monte Carlo simulated point spread functions. Eleven locations in the myocardium were chosen to generate PSFs and a distance-weighted PSF was generated from these for all other myocardial locations using MC-JOSEM (Ouyang et al., 2009). PSFs were generated for both ^{123}I and $^{99\text{m}}\text{Tc}$ radionuclides in both energy windows. All physical effects were included in the simulations, including Compton and coherent scatter, photoelectric absorption, and septal penetration by high-energy photons from iodine decays with an LEHR collimator.

Defects in the myocardium were parametrized by location, size, and severity (reduction in activity concentration compared with normal). Formally, the defect projection was a function of distance of defect from the myocardium base (z_0), height along the myocardial long-axis (h), angle subtended (ϕ), depth through myocardial wall (d), and defect severity (α). Figure 1 shows how the parameters were used. Note that defect parameters were the same for rest and stress sequential imaging, and rest sestamibi and rest BMIPP simultaneous imaging. Figure 2 displays three consecutive example transaxial and short-axis slices, displaying a septal defect.

Three defects were considered in this study, of differing location and size — (1) apical, (2) mid-ventricular septal, and (3) basal anterolateral. Table 1 describes the size and location of each defect. Defects were modelled to extend $d=75\%$ or 100% total wall depth, and to have two degrees of severity ($\alpha = 0.5, 0.75$). The apical defect was not used for TME discrimination due to the difficulty in defining wall depth at the apex. These studies resulted in four discrimination tasks for TME classification (two for each defect), and three for defect severity classification (one for each defect). Table 2 describes the classification tasks undertaken. For unaffected myocardium, the activity concentration was a single value, based on the clinical injected dose and known biodistribution of these tracers.

2.2. Optimal injected activity

The injected activities used in this study were chosen to reflect those commonly used in the clinic, however, they may not be the optimal injected activities for simultaneous imaging. Due to the cross-talk between the $^{99\text{m}}\text{Tc}$ and ^{123}I photopeaks, there is a balance between increasing injected activity leading to increased signal, and decreasing injected activity leading to less signal confusion. We determined the optimal injected activities for each radiopharmaceutical. Clearly, it is optimal from a signal-to-noise ratio perspective, to increase both activities indefinitely, since this would lead to higher counts, however, this is not feasible from a patient dosing perspective. Hence, we calculated the optimal injected activities, constraining the total number of decays to be equal to that with the currently-used

protocol. To achieve this, we defined an approximate measure, which was used to scale the two activities appropriately. This measure was:

$$D=At_{1/2}, \quad (2)$$

where A is the injected activity, and $t_{1/2}$ is the isotope half-life. This measure is related to absorbed dose, but does not include the energy deposited per photon. An increase in the injected activity of one isotope requires a decrease in the injected activity of the other, with a scaling factor equal to the ratio of their half-lives ($13.2/6.0=2.2$, for these isotopes).

Because we calculated optimal estimation precision for defect activity concentrations for both of the isotopes, we optimized the square of the defect activity concentration signal-to-noise ratios, viz.:

$$\text{SNR}^2 = \text{SNR}_{a_{Tc}} \times \text{SNR}_{a_{I}}. \quad (3)$$

2.3. Objective Analysis Tools

An objective comparison of simultaneous and sequential imaging can be achieved by considering the information carried by each imaging protocol about the parameters of interest: defect activity and transmural extent. The greater information carried by the data, the more precisely the parameter value can be estimated (van Trees, 1968). We use this minimum theoretical value (the Cramer-Rao lower bound) as a basis to evaluate the discrimination performance of simultaneous and sequential imaging.

2.3.1. Cramer-Rao lower bound—The Cramer-Rao lower bound (CRB) is the theoretical minimum variance of an unbiased parameter estimate (van Trees, 1968; Kay, 1993). It is expressed as the square-root of the diagonal components of the inverse of the Fisher information matrix (FIM), which for an N -length vector, θ , of unknown deterministic parameters, and Poisson statistics, has matrix entries given by:

$$J_{mn} = \sum_{ijkl} \frac{1}{P_{ijkl}(\vec{\theta})} \left(\frac{\partial P(\vec{\theta})}{\partial \theta_m} \right)_{ijkl} \left(\frac{\partial P(\vec{\theta})}{\partial \theta_n} \right)_{ijkl}, \quad (4)$$

where $m, n \in [1, N]$; (i, j) index projection pixels, (k) indexes projection angle and (l) indexes energy bin, and $P(\theta)$ is the expected projection dataset of the system. The simplest example of this is a one parameter model with one energy bin and one projection angle, where the CRB on the variance of the parameter, θ , is given by $1/\sum_i 1/N_i (dN_i/d\theta)^2$, where N_i is the number of counts in pixel i . For multiple parameters, a matrix is computed, with covariances between parameters. Inversion of this matrix therefore incorporates parameter covariances into the bounds (which are the square-roots of the diagonal matrix entries). In general, simultaneous estimation of multiple parameters leads to poorer precision on individual parameters, compared with estimating one parameter alone (this is not the case if there is no covariance between parameters — i.e., when there are no pixels in which both parameters affect the counts). We use projection data, rather than reconstructed images, because the projection data contain all the acquired information, without being affected by choice of reconstruction algorithm, image processing, or correction procedures (i.e., we understand the noise statistics of projections). We simultaneously estimate all parameters of the model — i.e., the FIM contains all of the unknown parameters (e.g., h, d, z_0, ϕ), yielding optimal

parameter precision values that incorporates the lack of knowledge we have about the myocardium, defect and background.

2.3.2. Binary classification task—To study the ability of the sequential or simultaneous protocol to discriminate between disease states (e.g., transmural defect versus sub-endocardial), we simulated mild defects. The Cramer-Rao lower bound on the precision of myocardial, background and defect parameters ($A_{Tc}, A_I, \phi_{Tc}, \phi_I, d_{Tc}, d_I, \alpha_{Tc}, \alpha_I, B_{Tc}, B_I$) was then computed. Defect severity estimation or defect wall depth estimation in each defect yielded two features (one for each of the two sequential studies, or one from each isotope in the simultaneous study) for each protocol upon which we performed a binary classification into a disease group. Using the correlated matrix of CRB values (the inverse of the FIM) for each parameter, we generated 5000 subjects in each disease stage by randomly sampling from the parameter covariance matrix and using the real parameter values as mean values. Then, for each subject, the likelihood of belonging to either of two groups was calculated, and a receiver operator characteristic (ROC) curve generated. Area under the ROC curve (AUC) was used as our performance metric for each protocol.

3. Results

3.1. Transmural extent of infarct

Table 3 displays the areas under the ROC curves for discriminating defects on the basis of transmural extent of infarct. Also shown is the statistical significance (p value) of differentiating simultaneous (full imaging time) from sequential imaging, and results for simultaneous imaging with the total imaging time halved (15 mins). Figure 3 displays the corresponding ROC curves. Simultaneous imaging yielded improved performance compared with sequential imaging for all cases studied. In addition, simultaneous imaging with reduced total time demonstrated comparable performance with sequential imaging. Although this seems counter-intuitive, it reflects the greater sensitivity of the scanner to ^{123}I photons and the higher myocardial extraction fraction of BMIPP, and therefore the increased rest iodine counts compared with the stress technetium counts.

3.2. Defect severity

Table 4 displays the areas under the ROC curves for discriminating defects on the basis of severity (α). Figure 4 displays the corresponding ROC curves, for the three defects studied. Performance for the apical defect is poor for all imaging protocols, due to the relatively small volume of this defect compared with the others studied. For this defect, and defect 3 (basal anterolateral), there is comparable discrimination performance (statistically indistinguishable) for simultaneous and sequential imaging. Only the mid-ventricular defect (defect 2) yielded improved simultaneous imaging performance.

3.3. Optimal injected activity

We calculated the square of the defect activity concentration signal-to-noise ratios for simultaneous imaging for defects 2 and 3. Figure 5 shows the results as a function of $^{99\text{m}}\text{Tc}$ -sestamibi (left) and ^{123}I -BMIPP injected activity. The optimal injected activities were higher for $^{99\text{m}}\text{Tc}$ -sestamibi (similar to stress injected activity) and lower for ^{123}I -BMIPP than those used routinely in the clinic, and the peak was weakly dependent on the size and location of the defect. The results demonstrate, however, that the performance improvement for optimal compared with the standard protocol is less than 10% using this measure.

4. Discussion

Simultaneous imaging yields comparable, and in some cases, improved performance compared with sequential imaging. For discriminating transmural from sub-endocardial infarcts, simultaneous imaging yielded improved performance, which was statistically significant for the sample of 5000 simulated subjects. For discriminating degrees of defect severity (reduction in activity concentration compared with normal myocardium), performance was comparable for the two protocols, except for the mid-ventricular defect, where simultaneous imaging yielded improved performance. In addition to the different volume of each defect, the different defect locations affect the results. Photon attenuation is greater for photons emitted from deeper within the body, and structures surrounding the myocardium affect photon propagation. We have also demonstrated that reducing the imaging time for simultaneous imaging to be that for a single study (15 mins) does not severely degrade performance, in many cases, and can provide comparable performance to sequential imaging in some cases.

These conclusions depend on the radiopharmaceuticals and injected activities used. SPECT scanners have a higher sensitivity to iodine photons than technetium photons, thereby improving the iodine signal. However, septal penetration of high-energy iodine decay photons in LEHR collimators leads to a poorer point spread function, thereby degrading the signal. In addition, there is the cross-talk between the closely-spaced photopeaks. Hence, it is unclear *a priori*, whether sequential or simultaneous imaging would yield better performance. It seems counter-intuitive that a 148 MBq (4 mCi) rest iodine signal would yield improved estimation performance compared with a 814 MBq (22 mCi) stress technetium signal, however there are three factors in the former's favour. Firstly, the myocardial extraction fraction of BMIPP is $5.4/1.2 = 4.5$ times that of sestamibi, thereby increasing counts in the myocardium. Secondly, because we are considering two energy windows for the simultaneous imaging, there are a significant number of iodine counts in the lower energy window (50% of the number of primaries in the higher energy window). Although these are scatter photons, the scatter is small (~ 10 keV) and so the PSF for these photons is not substantially degraded. Hence, this provides another factor of 1.5 increase in iodine counts. Thirdly, the sensitivity of the scanner to iodine photons is higher than for technetium photons, providing an additional factor of ~ 2 . These factors lead to ~ 2.5 times as many iodine counts as technetium counts in the myocardium. These are, of course, degraded by the broader PSF and the cross-talk, but our results demonstrate that this increase is sufficient for improved performance.

Figure 6 compares an example mid-ventricular transaxial slice for simultaneous and sequential imaging, to demonstrate the visual differences introduced by cross-talk. The simultaneous images (a, b) display the total counts (iodine + technetium) in each of the two energy windows, while the sequential image (c) displays the rest technetium counts in the lower energy window. Also displayed is a comparative plot of surface profiles for the three images (scaled to comparable counts), to demonstrate the increased point spread function of iodine compared with technetium, and the small impact on the lower energy window for simultaneous imaging, due to iodine contamination. The lower energy windows for simultaneous and sequential imaging (a, c) are visually similar. The simultaneous image has lower noise, due to the large number of iodine photons in the window, but also shows a broader point spread function due to septal penetration by high-energy iodine photons (see also, subfigure (d)). The upper energy window (b) demonstrates the increased myocardial extraction fraction of BMIPP compared with Sestamibi (higher myocardial to background contrast), and has little contamination from technetium photons.

A secondary issue is the injected activity for the stress perfusion scan. Typically, the rest and stress scans are performed on the same day, with a gap of a few hours to allow for the rest activity to decay. The increased stress injected activity, compared with rest, is used to increase the ratio of stress to remaining rest signal.

This study is fundamentally different to the Parkinson's disease brain study we have conducted (Trott and El Fakhri, 2008) because we have considered different isotopes for the sequential and simultaneous imaging protocols (in the brain study, both protocols used the same two isotopes to trace different functions), and the relative role of scatter, cross-talk and sensitivity to ^{123}I and $^{99\text{m}}\text{Tc}$ are dramatically different in brain and cardiac studies.

Changing isotopes or radiopharmaceuticals will affect these results, and therefore they should not be generalized to any dual-isotope cardiac imaging. However, this study demonstrates the feasibility, from a theoretical perspective, of simultaneous dual-isotope imaging in cardiac studies to trace two distinct functions while having the benefits of increased patient comfort, reduced scanner burden, and perfectly registered studies. We have not modelled imperfect image registration for sequential imaging in this work, but any mis-registration would be expected to reduce performance and/or introduce bias into the estimation process. Simultaneous imaging is novel, not only because of the reasons stated above, but also because this protocol removes the need to stress the patient, either physically or pharmacologically, thereby allowing the possibility of nuclear imaging in the emergency room.

Calculating the optimal injected activity for the two tracers for simultaneous imaging demonstrated that the precision with which defect severity can be measured is not strongly dependent on injected activity. In particular, the reduction in SNR^2 of a typical clinical protocol compared with the optimal activities, was less than 10%. This result allows some freedom in the clinician's choice of injected activity, which is typically influenced by many factors. Interestingly, the optimal technetium activity was substantially different from that used in this work (~900 MBq compared with 296 MBq), reflecting the shorter half-life of technetium compared with iodine, and the need to increase technetium counts to balance the iodine cross-talk signal.

This study has demonstrated the theoretical feasibility of simultaneous rest $^{99\text{m}}\text{Tc}$ -sestamibi, rest ^{123}I -BMIPP perfusion/fatty-acid metabolism in place of sequential rest/stress $^{99\text{m}}\text{Tc}$ -sestamibi perfusion imaging. This has been achieved by considering the information content of images using these two protocols, and demonstrating that simultaneous imaging yields sufficient information to estimate important parameters as precisely as sequential imaging. This study does not, however, comment on the physiological appropriateness of BMIPP fatty-acid imaging as a replacement for stress sestamibi perfusion imaging. We have taken the physiological equivalence of these two radiotracers as a starting point. It therefore serves as a basis for further study of these radiopharmaceuticals.

5. Conclusions

Simultaneous rest $^{99\text{m}}\text{Tc}$ -sestamibi, rest ^{123}I -BMIPP perfusion/fatty-acid metabolism cardiac studies are feasible for assessment of severity of defects and transmural extent of infarct, from the perspective of ideal estimation theory, and for three necrotic infarcts. Simultaneous imaging demonstrates comparable or improved performance compared with sequential imaging for discriminating simulated transmural from sub-endocardial infarcts, and defects of differing severity (reduction in activity from normal myocardium), when considering the information carried by the images. A wide range of injected activity values for the two radiotracers in simultaneous imaging produce activity estimation signal-to-noise

ratios within 10% of optimal, suggesting that the choice of injected activities does not strongly affect estimation performance.

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Figure 1. Cross-section (left) and surface display of the myocardial defect parameters, displaying the parameters describing the defect (d , h , ϕ).

Figure 2.
Example transaxial and short-axis slices through a reconstructed image (MLEM reconstruction) showing a septal defect.

(a) Defect 2 ($\phi=30^\circ$), $\alpha=0.5$ (b) Defect 2 ($\phi=30^\circ$), $\alpha=0.75$ (c) Defect 3 ($\phi=45^\circ$), $\alpha=0.5$ (d) Defect 3 ($\phi=45^\circ$), $\alpha=0.75$ **Figure 3.**

Receiver operator characteristic curves for discrimination between transmural ($d=100\%$) and sub-endocardial ($d=75\%$) defects, for the two defects studied, and for simultaneous and sequential imaging.

Figure 4. Receiver operator characteristic curves for discrimination between degrees of defect severity ($\alpha=0.5$ versus $\alpha=0.75$), for the three defects studied, and for simultaneous and sequential imaging.

Figure 5. Square of the defect activity concentration signal-to-noise ratios ($SNR_{Tc} \times SNR_I$) as a function of sestamibi (left) and BMIPP (right) injected activity, for two defects that were studied, and simultaneous imaging.

(a) Simultaneous imaging (lower energy window) (b) Simultaneous imaging (upper energy window) (c) Sequential imaging (lower energy window)

(d) Surface profile of images displayed

Figure 6. Example transaxial slices for simultaneous (a, b) and sequential (c) imaging, and scaled count profiles (d).

Table 1

Myocardial defect parameters used in this study.

Defect #	z_0	h	ϕ
	cm	cm	degrees
1	-8.5	0.85	360
2	-5.5	3.5	30
3	-2.5	2.5	45

Table 2

Myocardial defect severity and wall depth parameters used in the classification and discrimination tasks.

TME			
Defect #	α	d_1	d_2
		%	%
2	0.5	75	100
2	0.75	75	100
3	0.5	75	100
3	0.75	75	100
Severity			
Defect #	d	α_1	α_2
	%		
1	100	0.5	0.75
2	100	0.5	0.75
3	100	0.5	0.75

Discrimination performance for classification of transmural and sub-endocardial defects, for the two defects studied and two values of defect severity. Areas under the ROC curves and their uncertainties for 5000 simulated subjects, are displayed, along with the statistical significance of the difference in performance between simultaneous and sequential imaging. ‘Sim. (1/2)’ refers to simultaneous imaging with total imaging time halved (15 mins).

Table 3

Defect #	α	Sim.	Seq.	Sim. (1/2)	p
2	0.5	0.976±0.002	0.969±0.001	0.927±0.002	<0.001
2	0.75	0.788±0.005	0.728±0.005	0.765±0.005	<0.001
3	0.5	0.978±0.001	0.955±0.002	0.958±0.002	<0.001
3	0.75	0.759±0.005	0.726±0.005	0.700±0.006	<0.001

Discrimination performance for classification of defect severity, for the three defects studied. Areas under the ROC curves and their uncertainties for 5000 simulated subjects, are displayed, along with the statistical significance of the difference in performance between simultaneous and sequential imaging. ‘Sim. (1/2)’ refers to simultaneous imaging with total imaging time halved (15 mins).

Table 4

Defect #	Sim.	Seq.	Sim. (1/2)	p
1	0.777±0.005	0.780±0.005	0.773±0.005	0.41
2	0.968±0.002	0.960±0.002	0.916±0.002	<0.001
3	0.984±0.001	0.982±0.001	0.964±0.001	0.17