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End-expiration Respiratory Gating for a High Resolution Stationary Cardiac SPECT system

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Abstract

Respiratory and cardiac motions can degrade myocardial perfusion SPECT (MPS) image quality and reduce defect detection and quantitative accuracy. In this study, we developed a dual-respiratory and cardiac gating system for a high resolution fully stationary cardiac SPECT scanner in order to improve the image quality and defect detection. Respiratory motion was monitored using a compressive sensor pillow connected to a dual respiratory-cardiac gating box, which sends cardiac triggers only during end-expiration phases to the single cardiac trigger input on the SPECT scanners. The listmode data were rebinned retrospectively into end-expiration frames for respiratory motion reduction or 8 cardiac gates only during end-expiration phases to compensate for both respiratory and cardiac motions. The proposed method was first validated on a motion phantom in the presence and absence of multiple perfusion defects, and then applied on 11 patient studies with and without perfusion defects. In the normal phantom studies, the end-expiration gated SPECT (EXG-SPECT) reduced respiratory motion blur and increased myocardium to blood pool contrast by 51.2% as compared to the ungated images. The proposed method also yielded an average of 11.2% increase in myocardium to defect contrast as compared to the ungated images in the phantom studies with perfusion defects. In the patient studies, EXG-SPECT significantly improved the myocardium to blood pool contrast ($p < 0.005$) by 24% on average as compared to the ungated images, and led to improved perfusion uniformity across segments on polar maps for normal patients. For a patient with defect, EXG-SPECT improved the defect contrast and definition. The dual respiratory-cardiac gating further reduced the blurring effect, increased the myocardium to blood pool contrast significantly by 36% ($p < 0.05$) compared to EXG SPECT, and further improved defect characteristics and visualization of fine structures at the expense of increased noise on the patient with defect. The results showed that the proposed methods can effectively reduce motion blur in the images caused by both respiratory and cardiac motions,

which may lead to more accurate defect detection and quantifications. This approach can be easily adapted in routine clinical practice on currently available commercial systems.

Keywords

Respiratory motion; cardiac motion; SPECT/CT; dedicated cardiac SPECT

INTRODUCTION

Respiratory and cardiac motion are major degrading factors of image quality in myocardial perfusion imaging (MPI) with SPECT and PET since the images are acquired over extended periods with free breathing. The displacement of the heart caused by respiratory motion can exceed 20 mm (average 12-15 mm) in the superior-inferior direction (Teräs *et al.*, 2010; McLeish *et al.*, 2002). Previous studies have reported that respiratory and cardiac motion can cause; 1) reduction in myocardial activity in anterior and inferior walls leading to false-positive defects (Kovalski *et al.*, 2007; Buechel *et al.*, 2010; Kovalski *et al.*, 2009b; Pitman *et al.*, 2005); 2) bias in image quantification (Teräs *et al.*, 2010; Lucignani, 2009); 3) attenuation artifacts due to mismatched emission and CT attenuation scans (Dawood *et al.*, 2006; Wells *et al.*, 2010); and 4) motion artifacts and spatial blurring that may hinder defect detection (Yu-Wen *et al.*, 2009; Suzuki *et al.*, 2008).

The respiratory or dual gating approaches have been demonstrated to improve the image quality for PET images (Teräs *et al.*, 2010; Martinez-Möller *et al.*, 2007; Dawood *et al.*, 2008; Gigengack *et al.*, 2012; Büther *et al.*, 2009). However, the effects of respiratory motion were considered relatively minor for conventional SPECT MPI (Kovalski *et al.*, 2009a; Parker *et al.*, 2009). This is due to the fact that the effective spatial resolution of conventional SPECT (> 10 mm) and the respiratory-related cardiac displacements are of a similar order of magnitude. Secondly, in contrast to PET, which acquires all projection angles simultaneously, conventional SPECT systems use parallel-hole collimators and slowly rotating detectors that acquire data sequentially from multiple angles for 3-dimensional SPECT image reconstruction. Therefore, when the respiratory motion of a patient is irregular, projection data from all angular views are not available at all respiratory displacements, and this may cause reconstruction artifacts in amplitude gated images due to limited-angle reconstruction. These complex motion artifacts have been shown to limit the accuracy of motion estimation and thus have impacted respiratory motion correction algorithms (Dey *et al.*, 2010). Therefore, dual respiratory-cardiac gating is particularly challenging for conventional SPECT MPI.

Recently, a dedicated cardiac SPECT system (GE Discovery NM 530c and NM/CT 570c, GE Healthcare) has become commercially available. This system employs 19 detectors with pinhole collimators focused on the heart to perform stationary SPECT imaging (Bocher *et al.*, 2010). By using pixelated solid state CZT detectors and multiple pinhole collimators, it provides 5 mm spatial resolution at the center of the field of view, and a 5-7 fold improvement in sensitivity over conventional SPECT (Slomka *et al.*, 2009). The data acquisition of this system is fully stationary without camera rotation, providing complete-

angle reconstruction at any time interval. The high sensitivity feature also offers an opportunity to perform dual respiratory and cardiac gating through the extraction of a limited portion of SPECT listmode data without substantially increasing the image noise relative to conventional low-sensitivity step and shoot parallel-hole SPECT. For this system with 5 mm resolution and advanced reconstruction that incorporates collimator detector response (Bocher *et al.*, 2010), respiratory motion typically ranging 10 - 20 mm in amplitude can introduce significant artefacts and should be compensated to take the full advantage of high-resolution imaging (Kovalski *et al.*, 2009a).

In this study, we first developed respiratory monitoring and dual respiratory-cardiac gating systems for application with the high resolution fully stationary cardiac SPECT scanners. The gating system was designed to use the single cardiac gating input on the SPECT scanners to inject triggers carrying both respiratory and cardiac signals into the listmode data. Therefore, respiratory gating can be applied without making any hardware modifications on the current scanner. An offline rebinning program was developed to analyze the cardiac triggers recorded in the listmode data to rebin the data into end-expiration phases, or cardiac gated data only during the end-expiration phase for eliminating both respiratory and cardiac motions. We then used this gating system to investigate the impact of respiratory motion on defect detection and the effectiveness of end-expiration gating on compensating respiratory motion using physical phantoms and patient studies.

MATERIALS AND METHODS

Respiratory Motion Monitoring

A dual respiratory-cardiac gating box (Ivy Biomedical Systems, Branford, CT, USA) was developed to monitor motion (Liu *et al.*, 2011). With this dual gating system respiratory motion was detected by a compressive sensor pillow attached to the patient's abdomen for clinical studies, or on the programmable respiratory motion platform (QUASAR, Modus Medical Devices Inc., London, Ontario, Canada) used to hold the anthropomorphic torso phantom for the dynamic phantom studies, as illustrated in Figure 1(a). A respiratory signal was derived from the air pressure variations of the pillow and recorded at a sampling rate of 30 Hz by the gating box. The pillow has been previously validated against Anzai belt system (Anzai Medical, Tokyo, Japan) on healthy human volunteers (Chan *et al.*, 2012b). The ECG signal was also sent into the gating box as the second input as shown in Figure 1(b). These signals were then processed by the gating box prospectively and only cardiac triggers during end-expiration phases were sent to the ECG input of the stationary SPECT scanners (Discovery NM530c/570c, GE Healthcare), as described in the next section.

Respiratory Gating

A previous study demonstrated that a majority of patients tended to spend more time dwelling at end-expiration, and their breathing signals consistently returned to a similar location at end-expiration (Liu *et al.*, 2009). Therefore, data acquired during end-expiration can be considered as nearly respiratory motion free, and the use of end-expiration gating facilitates motion reduction while still preserving adequate count statistics (Liu *et al.*, 2010). In our implementation, the gating box determined the inspiration peak prospectively, and

considered 30% of the average cycle magnitude from previous three respiratory cycles as end-expiration period as highlighted by the blue rectangular box in Figure 2. The cardiac triggers (illustrated as the orange bars in Figure 2) were injected into the scanner gating input only during the end-expiration period. This end-expiration gating triggering is native to the gating box. However it can be turned off to only send cardiac triggers for regular cardiac gating. The current scanners only have one gating input to register the cardiac triggers into the listmode data acquisition. Therefore, to perform end-expiration gating, we analyzed the cardiac triggers in the listmode data by using an offline rebinning program. As shown in the bottom of Figure 2, several frequencies of the cardiac triggers can be obtained by plotting the ECG triggers into a histogram (x-axis is the interval between cardiac triggers, y-axis is the number of triggers registered for that interval). The short interval component reflects the R-to-R interval associated with a regular heart rate received during end-expiration period. The longer duration components correspond to the missing R wave triggers during the inspiration interval. As an example, a heart rate of 70 beat per minute implies an interval of 857 ms per beat, since the triggers were only sent during end-expiration, if the duration between two cardiac triggers $t_1-t_2 > \tau$, where τ is the threshold determined from the heart rate observed on the gating box, the intervals between t_1 and t_2 were considered to occur during inspiration. By discarding the data acquired during inspiration, the remaining listmode data were extracted as end-expiration gated data.

Dual respiratory and cardiac gating can also be achieved by performing additional cardiac phase gating on the extracted end-expiration data. For example, the end-expiration data can be rebinned into 8 cardiac gates to yield 8 listmode dataset, each of which is a dual respiratory and cardiac gated data. All the offline processed listmode data were stored on the system workstation (Xeleris™, GE Healthcare) and were rebinned into projections using the system's listmode processing software (Lister™, GE Healthcare). All datasets were reconstructed using maximum a posteriori (MAP) algorithm with Green's prior (Green, 1990), which is an edge preserving prior that encourages local smoothness while preserving prominent features. This prior is controlled by two user-specified parameters, the smoothing parameter β , and the edge preserving parameter α . Collimator detector response was also incorporated in the reconstruction. A 10% symmetrical energy window centered at 140 keV was applied during the rebinning process for technetium-99m (^{99m}Tc) images. No attenuation correction was performed for the dataset acquired on the stationary SPECT only system (Discovery NM530c, GE Healthcare). For the data acquired on the hybrid SPECT/64-slice CT scanner (Discovery NM/CT 570c, GE Healthcare) that employs CT based attenuation correction, the patients were directed to hold their breath at the end-expiration phase during the CT image acquisition. In addition, an attenuation correction quality control step was also performed using image alignment software (ACQC™, GE Healthcare) before reconstruction. This software allows users to manually adjust the alignment between individual SPECT and CT datasets to minimize the mismatch between images.

Validation of the End-expiration Gating

To validate the end-expiration gating that was achieved using the cardiac triggers stored in the listmode data, we compared the percentage of events retained during end-expiration

from the listmode data, and the percentage of time spent during expiration period from the respiratory traces and cardiac triggers exported from the dual gating box, for the patient studies that will be described in the following section. Note the end-expiration gating was achieved based on the cardiac triggers stored into the listmode data. The respiratory trace and triggers stored in the gating box were used for validation only in this study. The synchronization between the listmode acquisition and the respiratory trace recording was achieved manually by two operators, thus the start and stop time of these two datasets might not be perfectly aligned. However, the percentage of end-expiration duration computed from them was expected to be highly correlated.

Physical Phantom Studies

Two phantom scans were also performed using a Data Spectrum anthropomorphic torso phantom with cardiac inserts filled with ^{99m}Tc -Tetrofosmin. The first scan was to simulate a normal patient study (without defects) that was acquired on the stand alone stationary SPECT system (NM 530c). A total activity of ~ 185 MBq ^{99m}Tc was injected into the phantom. The activity-concentration ratios for myocardium:liver:background were 8:4:1. The blood pool was filled with water, and the lungs were filled with Styrofoam beads. To simulate respiratory motion, the phantom was positioned on a programmable respiratory motion platform that was driven by a regular patient respiratory trace with the mean amplitude of 13 mm (maximum amplitude of 30mm) in the superior-inferior direction across all cycles. The compressive motion sensor pillow from the dual gating box was attached to the holder of the platform that moves vertically to simulate the abdomen movement in the anterior-posterior direction during respiration (as shown in Figure 1(a)). The cardiac ECG signal was simulated at 70 beats per minute. A static motion-free dataset was first acquired as the ground truth followed by the motion scan. Both datasets were acquired for 6 minutes and reconstructed with the MAP algorithm and Green's prior using 80 iterations on the GE Xeleris workstation. The smoothing parameter β was set to 0.3 and the edge preserving parameter α was set to 0.41. No corrections for attenuation, and post-filtering were applied for this phantom. These parameters were different from those in the patient studies as discussed below to achieve higher resolution

In the second scan, the same torso phantom with a cardiac insert and three myocardial defects was used to simulate a patient with multiple perfusion abnormalities. This scan was acquired on the hybrid SPECT/CT system (NM 570c). A total activity of ~ 185 MBq of ^{99m}Tc was injected into the phantom. The concentration ratios among myocardium:liver:background were 10:10:1. Higher liver activity was used in this phantom to simulate patients with high subdiaphragmatic radiotracer activity. Two transmural defects (filled with air), each with a volume of approximately 4% of the entire myocardium volume was placed in the mid anterior wall, and in the septal wall towards the base. The third non-transmural defect (solid plastic, 50% wall thickness) was attached on the endomyocardium in the inferior wall. Figure 3 shows the fused SPECT and CT images in trans-axial, coronal and sagittal views to illustrate the locations and sizes of the defects. Note, as can be seen in the figure, the reconstruction volume of the SPECT images is smaller than the CT volume due to the relatively small field of view (FOV) of this SPECT system (~ 19 cm diameter) (Bocher *et al.*, 2010). The default matrix size of the reconstruction volume is $70 \times 70 \times 50$,

which is large enough to cover the FOV, but not the entire phantom. The small reconstruction volume may cause truncation artifacts particularly for objects with high radioactivity in the background (Chan *et al.*, 2012a). The SPECT images shown in Fig. 3 were reconstructed with an expanded system matrix ($120 \times 120 \times 120$) to minimize truncation artifacts for better visualization. All the phantom and patient studies presented in this manuscript, however, were reconstructed using the default system matrix to better resemble routine clinical practice. A patient respiratory trace [Figure 1(c)] with smaller mean amplitude of 11 mm across all cycles (maximum amplitude of 20 mm) was used to drive the phantom. The cardiac ECG signal was simulated at 70 beats per minute. The motion-free dataset was first acquired followed by a respiratory motion simulated acquisition. The static scan was acquired for 10 minutes, the respiratory scan was acquired for 15 minutes to generate motion corrected data. The attenuation CT was acquired at the end-expiration position where the motion of the platform was suspended. Images were reconstructed using the same reconstruction parameters as the normal phantom, although CT based attenuation correction was performed after SPECT and CT image alignment, as described above.

Patient Studies

Seven patients (6 male and 1 female) referred for ^{99m}Tc -Tetrofosmin hybrid SPECT/CT imaging underwent repeated SPECT/CT imaging with dual respiratory-cardiac gating. This study was approved by our institutional review board (IRB). Four patients were acquired for both stress and rest scans, and three patients were only imaged for stress studies (11 studies in total). The compressive sensor pillow was attached to the patients' abdomen prior to all the scans. The clinical acquisition (ECG only mode) was performed first followed by the CT acquisition for attenuation correction. The patients were asked to remain on the bed for another 4-6 minutes for the research acquisitions with the dual gating box. All the results shown in this study were generated from the research acquisitions. All patient dataset were reconstructed using MAP with Green's prior at 4 mm per voxel after SPECT and CT image alignment on the GE Xeleris workstation. Attenuation correction was incorporated in the reconstruction. The reconstruction parameters used to reconstruct Stress and Rest studies were: 60 iterations, $\beta = 0.3$, $\alpha = 0.41$, and 50 iterations, $\beta = 0.3$, $\alpha = 0.41$, respectively, for both NMC and EXG data. For dual respiratory-cardiac gated images, the parameters were set to 60 iterations, $\beta = 0.5$, $\alpha = 0.7$. A post-reconstruction Butterworth filter was applied to all the reconstructions with cutoff = 0.37 voxel^{-1} , order = 7. These parameters were employed based on a weight-based dose administration protocol, which also depends on the order of rest/stress studies used at the Yale-New Haven Hospital.

Data Analysis

For the phantom studies, the end-expiration gating images were compared to the reconstructions with no motion correction (NMC) and the static scans were used to serve as the ground truth. For the normal phantom, the performance of the proposed method was assessed quantitatively in terms of line profiles along short axis (SA) and the normal myocardium to blood pool contrast. The contrast ratio was defined as the ratio of the mean activity inside the ROIs drawn in the myocardium and blood pool. The ROIs were drawn on 3 consecutive slices in the anterior wall and blood pool on the vertical long axis (VLA)

images from the static acquisition. The same ROIs were also applied to the NMC and EXG images from the motion acquisitions.

For the phantom with defects, the quantitative evaluation was assessed using the contrast ratio between the mean activity derived from the ROIs drawn on the normal myocardium, defects, and blood pool. These ROIs were defined on the fused SPECT/CT images in the VLA view for the defects in the anterior and inferior walls, and SA view for the defects in the septal wall. The ROIs of the normal myocardium were defined in the anterior wall on the same slice as the defects. Similar to the normal phantom, each ROI mean value was obtained as the average of the ROI activities on 3 consecutive slices. In addition, 2D circumferential count profile plots derived on SA images at the level of the mid ventricle and base were also generated using Yale WLCQ software (Liu *et al.*, 1999). This 2D profile provides a semi quantitative assessment on defect size. The details of this quantification method (Yale WLCQ) have been previously described in (Liu *et al.*, 1999).

For the patient studies, as the breathing pattern and cardiac triggers were variable, in contrast to the phantom studies, fewer counts were expected to be retained in the EXG-SPECT images, leading to increased image noise. To separate the heterogeneity of uptake associated with the increase of noise from the effects of respiratory motion, we also compared the EXG-SPECT data with the images reconstructed with no motion correction at the matched level of counts (denoted as NMC-M). The NMC-M images were generated by rebinning the patient listmode data to a shorter acquisition to match the total number of counts retained in the EXG-SPECT data. We first compared NMC-M, EXG and dual respiratory-cardiac gated SPECT at diastolic phase (denoted as Dual Gated SPECT) on a patient with perfusion defects by visual assessment. The same patient was then assessed using the 2D circumferential count profile generated from Yale WLCQ software for defect size quantification similar to the phantom study. For quantitative assessments, we compared average normal myocardium to blood pool contrast for NMC-M SPECT, EXG SPECT, and Dual Gated SPECT across eleven studies. The ROIs were drawn on 3 consecutive slices in the normal myocardium and blood pool on the VLA slices of the NMC-M images. The same ROIs were also applied on the EXG images. For the Dual Gated SPECT, the ROIs were redrawn on the myocardium due to the thinner myocardium at diastolic phase. Paired t-test was used to compare the differences between the contrast ratios in these images. Finally, to assess the impact of respiratory motion and motion reduction on the uniformity of tracer distribution for patients with normal MPI, we derived an inter-segment variability metric based on a polar map. Eight normal studies out of eleven were used to compute this metric, while three studies were excluded due to the existence of defect, or apical hypertrophy in the heart. The polar map was divided into 9 segments and we calculated the percentage deviation of the mean value in each segment from the mean value in the mid-septal wall. The mid-septal wall was chosen as it was less affected by respiratory motion as will be shown in our phantom study (Figure 5). For a uniform polar map, the deviation in all the segments should be close to 0. This segmental deviation was then averaged across 8 patient studies as shown in the equation below.

$$SD_x (\%) = \frac{1}{N} \sum_n \left| \frac{\mu_x^n - \mu_{sep}^n}{\mu_{sep}^n} \right| \times 100\% \quad (1)$$

where SD_x is the segmental deviation in segment x , μ_x^n is the mean value in segment x of patient n , μ_{sep}^n is the reference mean value in the mid-septal wall of patient n , and N is the total number of patients.

RESULTS

Validation of the End-expiration Gating

A sample patient respiratory trace is shown in Figure 4(a), the circles denote the sharp transition points right after the inspiration peaks determined by the dual gating box prospectively, and the crosses denote the cardiac triggers that were injected into the listmode data. For the 7 studies whose respiratory traces were stored (4 respiratory traces were missing due to file corruption), the correlation between the percentage of end-expiration duration calculated from the listmode data, and the respiratory traces was $R^2=0.93$ as shown in Figure 4(b). The slight discrepancy between these two measurements was mainly due to the slight synchronization offset between the emission acquisition and trace recording that was achieved manually by two operators. This metric, however, validates the accuracy of the end-expiration rebinning based on the cardiac triggers stored in the listmode data.

Phantom Study – normal

The reconstructed images in the VLA, horizontal long axis (HLA), SA and trans-axial views of the normal phantom scans are shown in Figure 5(a). The static acquisition represents the ideal situation with no motion. It can be observed that the respiratory motion caused substantial blurring on the anterior and inferior walls in the VLA and SA images, potentially leading to false-positive defects, and spill-over of the activity from the liver into the neighboring myocardial region. The EXG-SPECT demonstrated reduced motion blurring and yielded higher myocardium to blood pool contrast than the NMC images, producing SPECT images that were visually similar to the static acquisition. The cross-talk from the liver was also suppressed. Since a patient-derived respiratory trace with regular breathing pattern and simulated cardiac ECG signal was used in this phantom acquisition, 4.2 out of 6 minutes data were retained in the end-expiration gate, and thus the image noise is visually similar to the static and NMC reconstructions. The quantitative profiles derived along the vertical and horizontal directions are shown in Figure 5(b) on the SA view. Note the radioactivity was lower in the inferior and septal walls as no attenuation correction was applied on this SPECT-only dataset. Compared to the static acquisition, it can be seen that the respiratory motion caused more radioactivity reduction in the anterior wall than in the inferior wall on the NMC images. This is because the loss of counts in the inferior wall due to motion blurring was artificially compensated by the spill-in of the counts from the liver. The radioactivity in lateral and septal walls was less affected by motion as the respiration was simulated in the inferior-superior direction only. The vertical profile also reveals a smaller blood pool size in the NMC images due to the spill-in of the counts from the myocardium. In contrast, the EXG-SPECT images recovered the radioactivity in

myocardium effectively, and yielded substantially thinner wall thickness as compared to the NMC images. The profile of the end-expiration gated image was nearly overlapped with the profile of the static image, indicating an effective respiratory motion reduction.

The changes associated with respiratory gating were evaluated quantitatively by assessment of the myocardium to blood pool contrast. These results are summarized in Table 1. The respiratory motion introduced a 63.8% reduction in contrast due to both a reduction of radioactivity in the myocardium and increased radioactivity in the blood pool. The end-expiration gating improved this difference by 51.2% to -12.6%.

Phantom study - with multiple defects

The reconstructions of the phantom with multiple defects are shown in different views [Figure 6(a)]. All the defects (denoted by the arrows) can be clearly identified in the static acquisition. In comparison, the myocardium appears to be more blurred due to the respiratory motion in the NMC-SPECT images. Spill-over of the counts from liver can also be observed in the VLA and SA views similar to the normal phantom scan. The contrast between normal myocardium and defects appear to be lower, and the non-transmural defect inserted in the inferior wall was blurred due to respiratory motion. This outcome represents a combined effect of the smaller defect size and the contamination of counts from the liver. In contrast, EXG-SPECT effectively reduced respiratory motion. All three defects appeared similar to the static acquisition. For this phantom study, 10.2 minutes out of 15 minutes of the data were retained in the rebinned end-expiration phase, which is similar to the duration of the static scan. Thus, the image noise is similar for both acquisitions.

The quantification of the defects size was first assessed using 2D circumferential count profiles generated with the Yale-CQ software (Liu *et al.*, 1999), and the results are shown in Figure 6(b). Profiles of the mid-ventricle and basal regions correspond to the locations of the transmural and non-transmural defects in the anterior and inferior walls, and the transmural defect in the septal wall, respectively. The profiles from the NMC and EXG-SPECT studies were compared to the static SPECT acquisition (see figure). The size of the non-transmural defect in the inferior wall was diminished in the mid-ventricle region of the NMC SPECT images. The basal profile plot demonstrated reduced radioactivity in the normal myocardium, and increased activity in the septal defect. These effects led to a decreased myocardium to defect contrast and reduced defect size. The motion was effectively reduced in the EXG-SPECT images, and yielded profiles similar to the static acquisition across regions with normal myocardium and in areas with defects.

The myocardium to defect and blood pool contrast ratios are presented in Table 2. In the NMC-SPECT images, the myocardium to defects contrast dropped 21.9% on average across all the defects, and the myocardium to blood pool ratio dropped 39.7 % as compared to the static scan. The use of EXG-SPECT imaging improved the average myocardium to defects contrast by 11.2% to -10.7%, and the myocardium to blood pool contrast by 27.4% to -12.3%.

Patient Studies

Table 3 summarizes the characteristics of the study population. For all patients, the average end-expiration duration was $35.0 \pm 6.6\%$ of the total scan time, which approximates a 1.4 minute scan for the 4 minute protocol, and 2.1 minute for the 6 minute protocol. Figure 7(a) shows a sample patient data reconstructed with no motion correction (100% counts) and with end-expiration gating at matched positions in each view. Similar to the phantom studies, it can be seen that the myocardium appeared to be sharper visually and has higher contrast between myocardium to blood pool with EXG-SPECT, although with higher image noise in the background and some noise blobs might be observed in the inferior wall. Note the right ventricle and atria also became more visible in the EXG-SPECT images. Quantitative profile analysis confirmed that an improvement of the myocardium to blood pool contrast ratio was achieved with EXG-SPECT (see Figure 7(b)).

Figure 8(a) illustrates the effects of EXG and dual gating on a sample patient with known defect and apical atrophy. Sample slices at matched location in the SA and VLA views are shown. Compared to the NMC-M images, the EXG-SPECT imaging provides better definition of the defect in the inferior wall (as denoted by the solid arrows) while dual respiratory and cardiac gated images further improved the defect definition and even fine structures (papillary muscle as denoted by the dotted arrow), in spite of reduced counts. Figure 8(b) shows the corresponding polar maps of the same patient. It can be seen that EXG yielded higher defect contrast than NMC-M. Dual gated image reveals a substantially larger defect than the other two methods. However, the polar map is also less uniform due to the increase of noise.

Figure 9 shows the quantification of the defect size in apical, mid-ventricle and basal regions of the same patient, generated by WLCQ. It can be seen that the EXG SPECT imaging yielded a bigger defect in the inferior wall and higher defect contrast than the NMC-M by eliminating respiratory motion, which echoes the results from the phantom study as shown in Figure 6. The dual gated method further increased the defect contrast and size than EXG by eliminating both respiratory and cardiac motions, albeit the curve is noisier.

Figure 10(a) shows the quantification results of normal myocardium to blood pool mean activity contrast ratio comparing NMC-M, EXG-SPECT and Dual Gated SPECT. The application of end-expiration gating improved the contrast ratio on all the patients, although had a variable response. This was probably due to the marked variation in the breathing patterns among the patients, and also the smaller cavity seen on patient 1 (studies 1 and 2) due to the apical hypertrophy. The dual gating approach further improved the contrast on 9 studies compared to EXG-SPECT except two studies, which might be due to the noise blobs inside the cavity of these two studies. As shown in Figure 10(b), the EXG-SPECT demonstrated a significant ($p < 0.005$) improvement in the contrast ratio. The increase from 4.38 to 5.43 represents a 24% increase across all the patients. The dual gated SPECT further improved the contrast significantly to 7.37, which represents a 68% improvement compared to NMC-M ($p < 0.005$), and 36% improvement compared to EXG ($p < 0.05$).

The evaluation of inter-segment variability obtained from 8 healthy studies is shown in Figure 11. It can be seen that NMC and NMC-M have similar variability across segments,

which shows that the reduction of counts did not affect the inter-segment uniformity. However, EXG yielded reduced variability in nearly all the regions (except basal-inferior) compared to NMC-M. This reduced variation across segments could be attributed to the reduction of motion as both reconstructions had similar number of counts. However, these differences are not statistically significant (paired t-test with $p < 0.05$ as statistical significant) in all the segments, which could be due to the small sample size.

DISCUSSION

In this study, we developed an end-expiration gating approach for application with a high sensitivity stationary CZT SPECT system. The proposed technique uses a single trigger input to carry both respiratory and cardiac signals, which can be readily adapted without hardware modification of the scanner, and requires minimal user interactions or data post-processing. By injecting the cardiac triggers only acquired at end-expiratory phases, the listmode data can be rebinned into end-expiration phase or dual respiratory-cardiac gated data retrospectively. Using both phantom and patient studies, we demonstrated that EXG SPECT improved image quality, quantification and defect characterization.

The proposed EXG SPECT method was first validated using a normal cardiac phantom, demonstrating improved myocardium to blood pool contrast compared to images acquired without motion correction. The EXG SPECT results closely resembled the static acquisitions. This phantom data were acquired on a SPECT-only system (GE 530c) that has a different triggering hardware interface from its SPECT/CT counterpart (GE 570c). Although without CT-based attenuation correction, this phantom study together with the defect phantom study acquired on the 570c system allowed us to evaluate our proposed triggering method for the interfaces on both 530c and 570c scanners. Additional cardiac phantom studies that incorporated multiple myocardial defects demonstrated improved characterization of both transmural and non-transmural defects achieved by EXG SPECT. Quantitative analyses revealed that EXG SPECT improved the myocardium-defects and myocardium-blood pool contrast ratios, and defect size quantification. Some residual bias was seen in the image contrast and quantification of defect size in both phantom studies, which could be attributed to intra-gate motion and inter-cycle variation as demonstrated in our prior PET studies (Chan *et al.*, 2013).

Application of the proposed method in patient studies significantly ($p < 0.005$) improved the myocardium to blood pool contrast as compared with the non-gated images. The average improvement in contrast was 24% across all the patients. Variation in the improvement in contrast across patients could be attributed to a combination of factors, including differences in the magnitude and pattern of breathing among the patients. In addition, our results show that EXG SPECT improved the characteristics of myocardium (Figure 7) and could lead to reduced inter-segment variability than the SPECT images with no motion correction at matched level of counts on normal patients (Figure 11). Indeed, previous studies also demonstrated that respiratory motion may create artifactual defects and heterogeneous perfusion, particularly in the anterior and inferior walls (König *et al.*, 2013; Pourmoghaddas *et al.*, 2013). On the other hand, for the patient with defects, respiratory caused blurring in defects leading to reduced defect contrast and size. EXG SPECT effectively reduced the

motion blur in the images and yielded increased quantitative defect size, which duplicated our phantom study where a static acquisition served as our ground truth measurement. These results show that respiratory motion might lead to false-positive or false-negative diagnosis, where application of EXG SPECT imaging can potentially be used as a method to improve both sensitivity and specificity.

By eliminating both respiratory and cardiac motion, the dual-gated approach further improved the average myocardium to blood pool contrast by 68% and 36%, compared to NMC-M and EXG results, respectively. For patient with defects, application of the dual gating further improved the definition of the myocardium wall, defect contrast, defect size quantification and the visualization of fine structures such as papillary muscle, which could not be seen without dual gating. A previous study (Suzuki *et al.*, 2008) also demonstrated that eliminating both respiratory and cardiac motion by using a motion-frozen technique yielded higher specificity compared to imaging with no motion correction, and resulted in a significant increase in overall accuracy for obese patients imaged on a conventional SPECT scanner with parallel holes collimator. Nonetheless, it would be more useful to evaluate the measurements of end-diastolic and end-systolic volumes, and ejection fraction (EF) determined with and without dual-gating. However, as shown in a recent study (Liu *et al.*, 2013), four most widely available commercial SPECT quantification software (Yale-WLCQ, Invia-Corridor4DM, Emory-Cardiac Toolbox and Cedars-Sinai-QGS) all generated significant underestimation of ejection fraction and bias in LV volumes, when applied on a phantom data acquired on this high resolution CZT camera. This is mainly due to the fact that the current software estimate these indices based on the partial volume effect (PVE) characterized for lower resolution NaI parallel-hole SPECT systems, but are not truly compatible with high resolution SPECT images with different PVE. As dual gating further improves the resolution (as shown in Figure 8), the change of EF and volumes may due to the confounding factors of improved resolution and/or bias in the calculation using these commercial software. The impacts of dual-gating on EF, therefore, warrant a more thorough investigation in the future.

One limitation of the proposed method is that the respiratory motion reduction was achieved at the expense of increased image noise due to the fact that only a portion of the counts were preserved in EXG SPECT images. The increased noise can lead to focal hot spots (noise blobs) and increased heterogeneity of perfusion locally that might mimic defects. In addition, the improvement of myocardium-blood pool contrast and myocardium-defect contrast might also be affected by image noise. The impact of noise could be assessed by rebinning the phantom acquisitions into multiple data sets, each corresponding to a different “noise realization”. By calculating the mean and standard deviation of contrast measurements, it could reveal the reproducibility of these metrics. However, as only 6 minutes of the normal phantom and 15 minutes of the defect phantom were acquired, 4.2 minutes and 10 minutes data were retained in the EXG data. Further rebinning the data into multiple datasets would cause substantial increase in noise even for 10 noise realizations (i.e. ~25 seconds acquisition per noise realization for the normal phantom). Therefore, we measured the reproducibility of the contrast measurement across 11 patient studies, and the uniformity across 8 healthy studies. Without knowing the ground truth, the results indicate

the contrast improvement was statistical significant, and the uniformity was improved compared to NMC-M by eliminating motion. Alternatively, as previous study (Herzog *et al.*, 2010) using a high sensitivity CZT detector system demonstrated that a 2 minute scan following a high dose (~900-1000 MBq) injection, and a 3 minute acquisition following a low dose (~300-350 MBq) injection yielded comparable image quality and clinical accuracy to a 15 minute scan acquired on a standard dual-head SPECT system, a count based criteria could potentially be established to moderately extend the acquisition time to compensate for the reduced count level associated with end-expiration gating. Nonetheless, a study that incorporates blinded human observer analysis in a larger population may be a more desired metric to evaluate the trade-off between motion reduction and increase of noise.

It should also be recognized that the retention of counts in the EXG-SPECT depends on both patient's breathing pattern and heart rate, since the end-expiration rebinning was achieved by analyzing the cardiac triggers injected prospectively. For both phantom studies, we used two respiratory traces that had regular breathing patterns and longer end-expiration duration, along with simulated ECG signal at 70 beat per minute to retain ~70% of the data. However, in the patient studies, as their breathing patterns were more irregular and heart rates varied during acquisitions, both of which affected the cardiac triggering, hence the percentage of counts retained in the EXG data was lower and had larger variations across patients (26 – 47%). In addition, this approach may yield sub-optimal EXG SPECT imaging results due to the estimation of the inspiration peaks that can be distorted by numerous factors, including; variation of respiratory patterns, change of motion amplitude, baseline shift, and the variation of heart rate. Some residual motion might have been left in the EXG SPECT images and/or fewer counts were retained due to this variability among patients. As a recent study demonstrated that retrospective rebinning could improve the consistency of phase gating for PET (Didierlaurent *et al.*, 2012), we expect the image quality can be further improved by more accurately defining the end-expiration period retrospectively. This issue would require further investigation.

The Dual Gated SPECT imaging approach improved the image resolution at the expense of substantially increased image noise. This is due to the fact that only 3-6% of the counts were preserved in each of the eight cardiac gated imaging bins during end-expiration. To compensate for the increased image noise associated with dual-gated imaging, grouping of the cardiac phases to form end-diastolic end-expiration rebinning or time varying cardiac gates (Teräs *et al.*, 2010) could also lead to improved image signal-to-noise ratio. Alternatively, images from different cardiac gates can be warped to match with a reference gate and then averaged subsequently (Slomka *et al.*, 2004). However, these approaches need to be applied with extra care as artifacts and non-uniformity may occur due to the inconsistencies between diastolic and systolic phases of the cardiac cycle. Ultimately, motion correction methods that use all the counts without increasing image noise should be developed. This could be achieved by incorporating motion information into the reconstruction in an event-by-event fashion (Chan *et al.*, 2013), as recently demonstrated in PET motion correction studies.

Finally, the proposed triggering approach could potentially be applied on other SPECT systems with conventional trigger rejection capabilities. These systems reject data if the

separation between two consecutive cardiac triggers is larger than a certain threshold of average cardiac cycle. When applying the dual gating box on those systems, the output data will intrinsically be end-expiration gated by rejecting inspiration data without the need of the offline trigger processing. We will investigate the applicability of the proposed method on other SPECT systems in the future.

CONCLUSION

In this study, we developed an external respiratory motion monitoring system and investigated end-expiration gating and a dual respiratory-cardiac gating approach for application with high-sensitivity stationary dedicated cardiac SPECT systems. The proposed gating method can effectively reduce respiratory motion blur, improve image quantification, and defect contrast and characterization for patients with abnormal perfusion. Although the improvement would depend on the variation of the respiratory pattern and amplitude of a given patient, the proposed end-expiration gating can potentially provide an adjunctive method for clinical SPECT imaging that would improve both sensitivity and specificity for detection of disease. However, this would need to be verified in a larger multicenter clinical trial using similar high sensitivity SPECT imaging systems.

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Figure 1.

(a) Illustration of the compressive sensor pillow attached on the abdomen of the patients that detects the respiratory motion, and the experiment setup for the phantom study. (b) The dual gating box with the compressive sensor pillow that records both the cardiac and respiratory signals, but sends only the ECG triggers to the scanner during end-expiration. (c) A representative patient respiratory trace used to drive the QUASAR motion platform in the second phantom experiment.

Figure 2.

The schematic illustrates the end-expiration ECG gating. The highlighted rectangular boxes denote the end-expiration period where the cardiac triggers (the orange bars) are injected in the listmode stream. The histogram of the cardiac triggers reveals multiple frequencies corresponding to the triggers injected at end-expiration (shorter intervals) and inspiration (longer intervals), respectively. A time threshold τ can be determined from the heart rate for the end-expiration rebinning.

Figure 3.

The fused SPECT/CT images of the defect phantom in standard views illustrate the locations and sizes of all the defects. The solid line arrows indicate the location of the transmural defects (air filled) in the septal and anterior walls. The dotted line arrow indicates the location of the nontransmural defect (solid insert) on the endocardial surface of the inferior wall. The non-transmural defect is not as well visualized as the transmural defects due to the smaller size. Note, the SPECT images are smaller than CT due to the smaller FOV and reconstruction matrix size of the SPECT scanner.

Figure 4.

(a) A sample patient respiratory trace exported from the dual gating box. The circles denote the sharp transition points right after the inspiration peaks determined by the dual gating box prospectively, and the crosses denote the cardiac triggers that were injected into the listmode data. (b) The correlation between the percentages of end-expiration period calculated from the listmode data, and the respiratory traces on 7 patient studies. The discrepancy between these two measurements was mainly due to the synchronization between the emission acquisition and trace recording achieved manually by two operators, and slight synchronization offset between these two acquisitions occurred in some studies.

Figure 5.

(a) The reconstructed images of the normal phantom in standard views. The dotted arrow denotes the region that was contaminated by the spill-out activity from the liver. (b) Count profiles from phantom along the vertical (top) and horizontal (bottom) arrows shown on the SA view. The greatest improvement of the myocardium to blood pool contrast is achieved by EXG-SPECT in the vertical direction, which was the primary direction of the phantom motion.

Figure 6.

(a) The reconstructed images of the phantom with defects in standard views. The anterior (solid blue), inferior (dashed yellow) and septal (dotted green) wall defects are denoted by the colored arrows. (b) The circumferential count profiles of Static vs NMC-SPECT (left), and Static vs EXGSPECT (right). The yellow solid arrows denote the location of the defects, and white dotted arrows denote the reduced activity in normal myocardium due to respiratory motion.

Figure 7.

(a) The myocardial perfusion images of a representative patient in standard views. This patient was injected with 577 MBq ^{99m}Tc -tetrofosmin and imaged for 4 mins. 36% counts were preserved in the EXG-SPECT images. Note 100% counts were used in the NMC images to illustrate the increase of noise due to reduced counts. The solid arrows denote the right ventricle that became better visualized in the EXG-SPECT images. (b) Count profiles for the horizontal and vertical lines drawn on the SA view demonstrate the improvement of the myocardium to blood pool contrast achieved with EXG-SPECT imaging.

Figure 8.

Myocardial perfusion images of a representative patient showing a moderate sized defect (denoted by the solid arrows) extending from the mid-ventricle to the base. The images are shown in (a) SA view (top), VLA view (bottom), and (b) polar maps. The end-diastolic phase is shown for the dual gated images. The defect was blurred by respiratory motion in the NMC-M SPECT images. EXGSPECT and dual gated-SPECT yielded a better contrast resolution within the defect. Note the papillary muscle (denoted by the dotted arrow) is only visualized in the dual gated images demonstrating the effectiveness of respiratory and cardiac motion reduction achieved by dual gating. However, dual-gating also yielded a less uniform polar map due to the increase of noise in (b).

Figure 9.

Circumferential count profiles of (a) NMC-M (yellow) vs EXG (red) SPECT images, and (b) NMC-M (yellow) vs Dual Gated (red) SPECT images at apical, mid-ventricle, and basal levels for the same patient as shown in Fig. 8. The yellow solid arrows denote the defect. The dashed horizontal lines show the smallest % of maximum achieved by the EXG-SPECT to aid the comparison between EXG and Dual Gated SPECT. The defect size was diminished in the NMC-M SPECT images due to respiratory motion. EXG reduced respiratory motion and yielded a more pronounced defect. Dual-gating revealed an even increased defect size by reducing both respiratory and cardiac motions.

Figure 10.

(a) The myocardium to blood pool contrast for all the patients. The definitions of the ROIs in the myocardium and blood pool are overlaid on a sample VLA slice in the top left corner. (b) EXGSPECT and dual gated SPECT improved the mean contrast from 4.38 to 5.43, and 7.37 across 11 patients compared to NMC, respectively. Data are expressed as mean $\pm$ SEM. * $p < 0.05$. ** $p < 0.005$.

Figure 11.

Inter-segment variability measurement across 8 normal studies. On each polar map, the inner, middle and outer rings correspond to apical, mid-ventricle and basal regions, respectively. The value in each segment denotes the percentage deviation of its mean value from the mid-septal wall averaged across 8 normal studies. A uniform polar map should have similar mean value in all the segments, thus smaller deviations. It can be seen that NMC 100 and NMC-M yielded similar variability in all the segments, while EXG yielded less variability than NMC-M in all the regions except in the basal inferior wall.

TABLE 1

Myocardium to blood pool contrast ratio of the normal phantom scan. The percentage changes comparing to the static acquisition are shown in the parentheses

Static-SPECT	NMC-SPECT	EXG-SPECT
13.6	5.3 (−63.8%)	11.8 (−12.6%)

TABLE 2

Myocardium to defects and blood pool contrast ratio of the phantom scan with defects. The percentage changes comparing to the static acquisition are shown in the parentheses.

	Static	NMC	EXG
Myocardium/Septal wall defect (transmural)	2.39	1.81(−24.1%)	2.13 (−10.7%)
Myocardium/Anterior wall defect (transmural)	2.51	1.99 (−20.8%)	2.25 (−10.5%)
Myocardium/Inferior wall defect (non-Transmural)	1.92	1.52 (−20.8%)	1.71 (−10.8%)
Mean	2.27	1.77 (−21.9%)	2.03 (−10.7%)
Myocardium/Blood Pool	5.62	3.39 (−39.7%)	4.93 (−12.3%)

TABLE 3

Characteristic of patients in this study. The study includes 7 males and 1 female patient.

Characteristic	Mean $\pm$ SD	Range
Age (Year)	56.8 $\pm$ 14.9	45 - 84
BMI	31.9 $\pm$ 4.3	28.7 - 39.5
Dose (MBq)	617.9 $\pm$ 234.2	347.8 – 1024.9
Preserved counts in EXG (%)	35.0 $\pm$ 6.6	26 - 47