A Comparison of Strategies for Summing Gated Myocardial Perfusion SPECT: Are False Negatives a Potential Problem?

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Citation

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Abstract

Introduction: The impact of technical difficulties on the diagnostic integrity of myocardial perfusion SPECT have been well documented, however, their impact on gated myocardial perfusion SPECT has more significant implications. In theory, the generation of the standard ungated data set is just summation of all the intervals for each projection from the gated data set. The reconstruction strategy employed may be stream-lined to reduce the computational demands of gated SPECT reconstruction and, thus, may potentially rendering it less accurate than it would have been without gating.

Methodology: The research design employed a retrospective repeat-measures design. Using this approach meant that a single clinical data set acted as both the control group and the experimental group. 45 rest/stress patient files were examined quantitatively with CEqual quantitation software for reconstructed ungated data and summed data post reconstruction of the gated data. For each individual study, the two methods of reconstruction were performed simultaneously as a 'batch' to ensure identical reconstruction parameters and slice orientation.

Results: Compared to data reconstructed as ungated files, summation of reconstructed gated files results in; a decrease in defect extent by 20.4%, a decrease in defect severity by 13.6%, a decrease in left ventricular lumen by 19.2%, an increase in total heart diameter by 9.8% and an increase in wall thickness by 32.3%.

Conclusion: Not only does the generation of perfusion data via summation of the reconstructed gated data fail to provide the anticipated relief in computational demands of gated SPECT reconstruction, but it also introduces potential false negative results for coronary artery disease. This potential problem results from over smoothing and this may be particularly problematic in detecting small or non transmural defects clinically. This potential is extended to include disease classification inaccuracies resulting from underestimation of the size and/or extent of detected defects.

INTRODUCTION

A major limitation of reconstruction filters in SPECT is that optimal filters for qualitative or visual evaluation may be quite different from optimal filters for quantitation. This means the study requires reconstruction twice or a ‘compromise filter' needs to be employed. The most appropriate filter for quantitation of gated data may be quite different from that of the qualitative assessment of ungated data. Filter specifications are optimized for individual data sets and, therefore, software utilizing default filter values (order, cut-off) require specific acquisition parameters (i.e. acquisition matrix, time per projection, number of projections, patient dose etc.) and assume a standard biodistribution. Unfortunately, the optimal filter may not be employed for many patients, for example, those patients with little attenuation causing higher count densities than ‘normal' or those obese patients with lower count densities than ‘normal'.

Despite these limitations it is universally recommended that default filter parameters are adhered to due to the danger of introducing false positive or false negative results following filter customization ([1]). Over filtering myocardial perfusion SPECT data is known to cause false negative results ([1]). Since the major quantitative software packages to determine functional parameters in gated SPECT rely on edge detection, filtering errors will also cause inaccuracies in

these calculations.

The myocardial perfusion data are processed in two ways. Firstly the gated data are ‘ungated' (i.e. all the data contained in gated bins are combined into one image per projection) and reconstructed using the standard filtered back projection technique. Using a transverse image the myocardium is reorientated to obtain the three standard imaging planes used in nuclear cardiology for qualitative evaluation; short axis, vertical long and horizontal long axis. The second part of the processing technique is to reconstruct the gated file (i.e. the file containing the information collected in the eight bins). The reconstructed gated SPECT data can be displayed as a rotating cinematic loop allowing visual evaluation of ventricular wall motion and thickening of the left ventricle. The ventricular EF, EDV and ESV can be calculated separately by several types of commercially available automated programs.

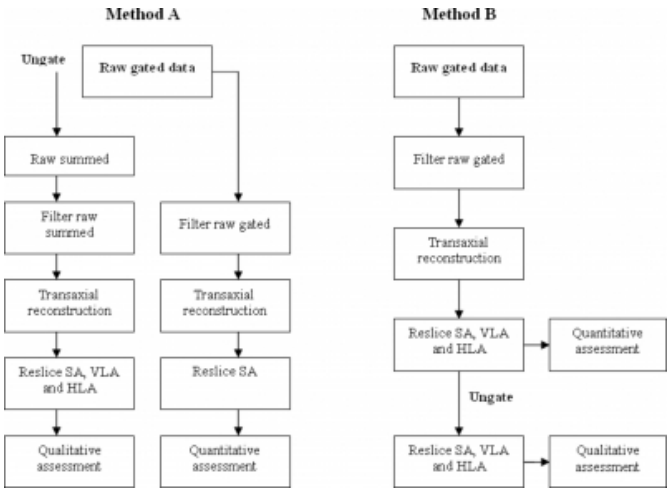
The reconstruction strategy employed may be stream-lined to reduce the computational demands of gated SPECT reconstruction and, thus, may be a potential source of false negative findings in the ungated qualitative image set. While the cost of computer storage and power has decreased significantly in recent years, it still plays a major role in processing strategies ([2]). There are a number of data sets generated by acquisition and processing in gated SPECT. The size of the raw gated data set increases proportionally to the number of intervals collected, raising the processing time and storage space requirements.

One of the main advantages of gated SPECT acquisitions is the ability to generate an ungated data set, thus, providing a normal myocardial perfusion SPECT data set for perfusion assessment and the functional gated data. This does, however, rely on appropriate handling of rejected beats. Quite simply, summation of all intervals and the rejected beats bin for each projection results in a typical ungated SPECT data set. There are a number of strategies employed for processing the gated and ungated data sets:

- The gated data set is summed to produce the ungated data set and each is independently reconstructed (Figure 1; method A). This is the method loosely referred to in a number of texts (2,3) but results in increased processing time and storage requirements.
- The gated data set is reconstructed to produce short axis, vertical long axis and horizontal long axis files whose intervals are subsequently summed to produce an ungated image data set (Figure 1, method B). This strategy is employed by 31.1% (95% CI 22.5% to 41.3%) of Nuclear Medicine departments in Australia (4).

Figure 1

Figure 1: Processing algorithms for gated SPECT. Abbreviations include; short axis (SA), vertical long axis (VLA) and horizontal long axis (HLA).



There are no guidelines or protocols published that describe the appropriate strategy for gated SPECT reconstruction. Intuitively, the gated dataset should be ungated prior to the filtering process to generate the traditional image dataset to avoid displaying images that have been filtered eight times (the number of gate intervals). While DePuey ([3]) and Germano & Berman ([2]) have published flow charts suggesting the use of method A (Fig. 1), there is no evidence or discussion in the literature supporting this proposition. This choice, one suspects, represents a convenience rather than efficiency given current available computer hardware and that method A does not require processing of gated VLA and HLA slices. Method B results in summation of previously filtered low count slices to produce an ungated perfusion data set which may result in an over ‘smoothed' image, introducing the potential to remove ‘real' defects from clinical data.

THE RESEARCH QUESTION

Does the generation of a standard myocardial perfusion image data set by ‘ungating' the reconstructed cardiac slices of the gated SPECT data result in over filtering the perfusion data and, thus, potentially introduce false negative results?

METHODS

All data were acquired following two day stress/rest or two day rest/stress myocardial perfusion SPECT protocols. All myocardial perfusion SPECT studies employed a 740 MBq dose of ^{99m} Tc tetrofosmin (Nycomed-Amersham, Amsterdam). A triple detector gantry was used to acquire all patient data. All data acquisitions employed low energy, high resolution collimation with step and shoot mode, elliptical orbits, and a 64 matrix. The zoom was 1.23 and projections were acquired at 3 degree intervals for 20 seconds per projection to provide a total acquisition time of 15 minutes. All patients were positioned supine with their feet into the gantry for an eight interval gated SPECT acquisition. Beat rejection employed a variable window width and, thus, perfusion data was not compromised by beat rejection. All data was reconstructed using a 180 degree filtered back projection algorithm.

A total of 50 patient files were examined, each with both a gated rest and gated stress study and, thus, a total of 200 studies were produced for quantitative analysis with CEqual quantitation software. Approval was granted by the Charles Sturt University Ethics in Human Research Committee for the retrospective manipulation of the patient data.

The gated SPECT data were reconstructed as both gated and ungated data sets to produce short axis slices. For each individual study, the two methods of reconstruction were performed simultaneously as a ‘batch' to ensure identical reconstruction parameters and slice orientation. The following reconstruction procedure was applied to the control group (method A; Fig. 1):

- The gated data set was ungated to produce a conventional SPECT data set.
- The stress studies were pre-filtered with a Butterworth low pass filter (order 5.0 and cut-off 0.33 cycles/pixel).
- Rest studies were pre-filtered with a Butterworth low pass filter (order 5.0 and cut-off 0.25 cycles/pixel).
- Reorientation of the transverse slices to accommodate cardiac orientation resulted in generation of short axis slices for CEqual quantitation employing a ‘two day MIBI' normal database.

The following reconstruction procedure was applied to the experimental group (method B; Fig. 1):

- All studies were pre-filtered with a Butterworth low pass filter (order 5.0 and cut-off 0.21 cycles/pixel).
- Reorientation of the transverse slices to accommodate cardiac orientation resulted in generation of short axis slices.
- Each set of three sets projection slices were then ungated.
- The short axis slices were then analyzed using CEqual quantitation software employing a ‘two day MIBI' normal database.

The CEqual quantitative analysis software was used to evaluate and compare each control dataset with the experimental data set. For each short axis slice generated (n = 200), the location, extent and severity of defects was recorded and compared for method A and method B. The percentage extent of the defects represented the percentage of pixels that fell below the normal limit threshold. The severity of each defect represented the summation of the values derived from multiplying each of the standard deviations below the normal range (i.e. one through eight) by the number of pixels which are calculated to be that number of standard deviations below the normal range.

The statistical significance was calculated using Chi-Square analysis for nominal data and Student's t test for continuous data. A P value less than 0.05 was considered significant. The differences between independent means and proportions was calculated with a 95% confidence interval (CI). Correlation was evaluated with Chi-Square analysis and reliability measured using Cohen's Kappa coefficient. Bland-Altman analysis ($_5$) and the matched pairs t test were used to assess agreement between paired data. Normality of distribution was assessed using the Shapiro-Wilk W test.

RESULTS

All 50 clinical studies had both stress and rest data quantitated with CEqual software following reconstruction by both methods A and B (Fig. 1). Of the 50 patients, 25 were male and 25 were female. The mean patient age was 67.3 years with a range of 46 to 85 years. The CEqual results reported no defects in either method A or method B data in 5

patients (10%) and, thus, these patients were excluded from the investigation. The remaining 45 patient files had a gender distribution of 53.3% female (24) and 46.7% male (21) (P = 0.66). The age distribution was normally distributed (P = 0.14) with a mean of 67.8 years and a range of 45 years to 85 years. Defect extent and severity are summarized in table 1.

Figure 2

Table 1: Summary of defect extent and severity results with respect to the two methods of summation.

Method	Mean Extent (%*)	Range (%*)	Mean Severity (SDs**)	Range (SDs**)
A	16.1	4 to 45	-639.1	-2527 to -85
B	13.6	1 to 45	-555.4	-2505 to -23

* Denotes percentage of total myocardium.
** Denotes standard deviations below the normal data base.

EXTENT OF DEFECTS

No statistically significant relationship was noted between defect extent and patient age (P = 0.30). A statistically significant difference was noted in the defect extent between males (mean 15.8% with 95% CI of 13.6 – 18.0) and females (mean 10.4% with 95% CI of 8.3 – 12.4) (P < 0.001). No statistically significant difference was noted between the mean defect extent determined on stress studies compared to those determined on rest studies for either method A (P = 0.05) or method B (P = 0.13).

No statistically significant relationship was noted between the absolute extent difference (method A – method B) and age (P = 0.14), gender (P = 0.78) or study type (P = 0.14). No statistically significant relationship was noted between the percentage extent difference (difference / method A) and age (P = 0.72), gender (P = 0.29) or study type (P = 0.70). The mean difference between methods A and B for defect extent was 1.9% (95% CI 1.2 – 2.6). Consistent with the statistically significant difference noted between matched pairs (P < 0.001), a statistically significant difference was also noted comparing this mean difference to a hypothetical difference of zero (P < 0.001). Similarly, the mean difference expressed as a percentage change from method A to method B was 20.4% (95% CI 10.9 – 29.9) which showed a statistically significant variation from the hypothetical mean of zero (P < 0.001) and a statistically significant difference between matched pairs (P < 0.001). These statistically significant differences are supported by the lack of zero within the 95% CIs.

SEVERITY OF DEFECTS

No statistically significant relationship was noted between defect severity and patient age (P = 0.37). A statistically significant difference was noted in the defect severity between females (mean -387.8 with 95% CI of -492.4 to -283.2) and males (mean -714.4 with 95% CI of -826.2 to -602.5) (P < 0.001). No statistically significant difference was noted between the mean defect severity determined on stress studies compared to those determined on rest studies for either method A (P = 0.27) or method B (P = 0.38).

No statistically significant relationship was noted between the absolute severity difference (method A – method B) and age (P = 0.17), gender (P = 0.92) or study type (P = 0.17). No statistically significant relationship was noted between the percentage severity difference (difference / method A) and age (P = 0.30), gender (P = 0.51) or study type (P = 0.14). The mean difference between methods A and B for defect severity was 68.9 standard deviations below the normal data base (95% CI 47.5 – 90.2) where method B demonstrated a tendency toward less severe defects. Consistent with the statistically significant difference noted between matched pairs (P < 0.001), a statistically significant difference was also noted comparing this mean difference to a hypothetical difference of zero (P < 0.001). Similarly, the mean difference expressed as a percentage change from method A to method B was 13.6% (95% CI 3.4 – 23.7) which showed a statistically significant variation from the hypothetical mean of zero (P < 0.01) and a statistically significant difference between matched pairs (P < 0.001). These statistically significant differences were again supported by the lack of zero within the 95% CI.

SPATIAL MEASURES

Spatial measures were performed on the mid short axis slices of 12 consecutive patients. Identical slices and reference points were used between method A and method B. Of the 12 patients, 8 (66.7%) were female and 4 (33.3%) were male. The mean age of this subset of patients was 69.6 years with a range of 46 years to 84 years.

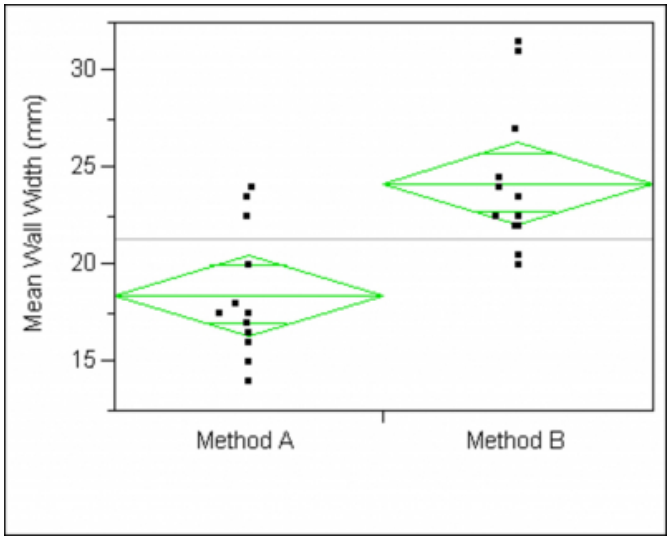
A statistically significant difference was noted between the left ventricular lumen short axis dimensions measured by method A and method B matched pairs (P < 0.001). The mean left ventricular lumen diameter for short axis slices generated by method A was 26.4 mm (95% CI 21.3 mm – 31.5 mm) and for method B was 21.0 mm (95% CI 15.9 mm – 26.1 mm). The mean difference between methods A and B for the short axis left ventricular lumen diameter was 5.0 mm (95% CI 3.8 mm – 6.2 mm) and as a percentage, 19.2% (13.1% - 25.3%) (P < 0.001).

A statistically significant difference was also noted for the mean left ventricular short axis diameter between matched pairs ($P < 0.001$). The mean left ventricular short axis diameter for slices generated by method A was 63.3 mm (95% CI 58.3 mm – 68.3 mm) and for method B was 69.5 mm (95% CI 64.5 mm – 74.5 mm). The mean difference between methods A and B for the short axis left ventricular diameter was 6.2 mm (95% CI 4.4 mm – 7.9 mm) and as a percentage, 9.8% (7.2% - 12.4%) ($P < 0.001$).

These calculations were used to determine the mean wall thickness. One should note that the following calculations are means and do not reflect the physical, physiological or scintigraphic variations in wall thickness in any one left ventricle. A statistically significant difference was noted between mean wall thickness matched pairs ($P < 0.001$). The mean left ventricular wall thickness for short axis slices generated by method A was 18.5 mm (95% CI 16.3 mm – 20.5 mm) and for method B was 24.3 mm (95% CI 22.1 mm – 26.4 mm). Consistent with the lack of overlap of 95% CIs, a statistically significant difference was shown between the means ($P < 0.001$) (Fig. 2). The mean difference between methods A and B for the short axis left ventricular wall thickness was 5.8 mm (95% CI 4.7 mm – 6.9 mm) and as a percentage, 32.3% (25.5% - 39.2%) ($P < 0.001$).

Figure 3

Figure 2: One way Anova analysis of the mean wall thickness comparing methods A and B. Note the lack of overlap of 95% CIs denoted by the vertical extent of the diamond overlays.



DISCUSSION

The widespread use of gated myocardial perfusion SPECT combined with its relatively recent development warrants optimization of the processing protocols used to ensure diagnostic integrity. The increased value of gated myocardial perfusion SPECT, with its ability to combine functional information and myocardial perfusion is without debate. It allows both regional perfusion and global function to be assessed simultaneously with neither additional cost nor added acquisition time ([6,7]). Unfortunately, the generation of an acceptable (rather than optimized) conventional data set from the gated data may be the adopted philosophy (as outlined by method B in Fig. 1). It is paramount that the inclusion of gating in myocardial perfusion SPECT does not compromise the integrity of the perfusion data and this philosophy should extend to data reconstruction and processing. The functional information is a supplement to the perfusion data.

The reconstruction strategy employed may be stream-lined to reduce the computational demands of gated SPECT reconstruction and, thus, may be a potential source of false negative findings in the ungated qualitative image set. The cost of computer storage and power has decreased significantly in recent years however it still plays a major role in processing strategies ([2]). As many as 31.1% of departments in Australia employ method B to reconstruct their myocardial perfusion studies ([4]). One suspects that this potential problem has wider international implications since at least one major gamma camera manufacturer has, until recently, included method B as the generic processing macro accompanying QGS software installations. In effect, this method of reconstruction results in each of the 8 bins (or number of gate intervals) being independently filtered prior to summing, with the resultant file then used for qualitative assessment. Intuitively, this approach would result in over filtering the perfusion data. Over filtering of myocardial perfusion SPECT data is known to cause false negative results ([8]). Furthermore, the low count nature of gated SPECT with each projection set reduced in counts by a factor equal to the number of collected intervals means that image quality is adversely affected by noise. Noise is more problematic in low count studies so gated SPECT studies can significantly benefit from appropriate image filtering and processing. The low count data from gated studies results in data with low statistical certainty ([9]).

The authors recognize that filtering is a linear process and that, in theory, identical filters should result in the same outcome for both method A and method B. In reality,

however, the same filters are not employed because the initial filtering operation serves very different roles. In the case of method A, filtering is optimized for either QGS or for the summed perfusion data. Method B, however, employs a filter for perfusion data that is designed for QGS analysis. If method B employed a filter suitable for generating perfusion data, the gated filtered files would be rendered worthless.

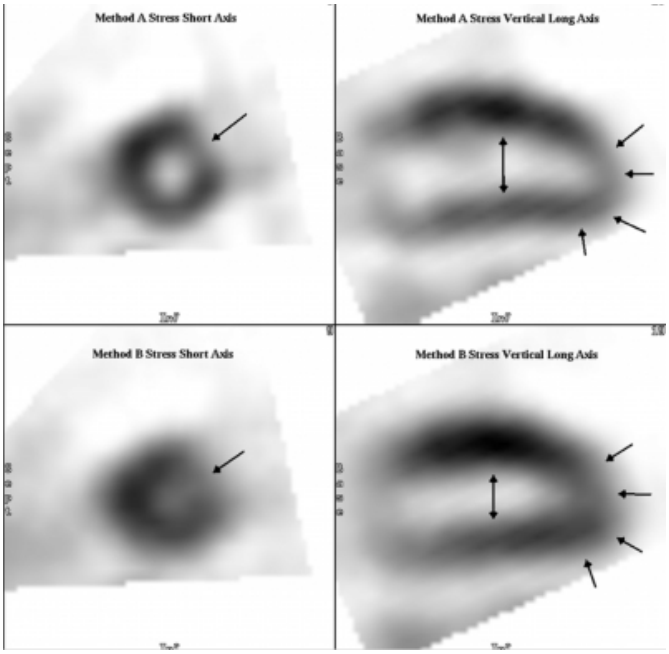
In this study, a statistically significant difference was noted in both the defect extent and the defect severity between males and females ($P < 0.001$ for each). This observation may simply reflect more severe coronary artery disease in males. It was a little surprising to note that there was no statistically significant difference for defect extent and severity between rest and stress studies. The lower corresponding mean defect extent and severity most probably reflects reversibility of defects (ischemia), however, the lack of statistically significant difference may reflect the combination of a prevalence of infarction and artefacts in the sampled cohort (fixed defects).

The mean difference for defect extent between method A and method B was 1.9% of the myocardium (95% CI 1.2 – 2.6%) where a positive value indicates method A as greater defect extent. This difference was deemed statistically significant ($P < 0.001$) which is supported by the lack of zero in the 95% CI. This percentage difference is a little difficult to interpret because defect extent within the sample varied substantially. Thus, the percentage change from method A to method B was evaluated to explore the relationship. It was noted that, on average, method B produced defects of an extent 20.4% smaller than corresponding defects on method A. Similarly, the difference in defect severity between method A and method B was statistically significant ($P < 0.001$) with, on average, method B producing defects of a severity 13.6% smaller than corresponding defects on method A. These observations introduce a serious interpretation dilemma. There is potential for larger defects or severe defects to be underestimated by 20% and 14% respectively which may reclassify the extent and/or severity of disease. More importantly, however, small defects (especially non transmural defects or low severity defects) may be reduced beyond the systems resolving power and pass undetected. This interpretation dilemma may be compounded by the observation that defect extent and severity have a strong negative correlation. Thus, as extent worsens, typically so does defect severity resulting in the impact of method B reconstruction increasing the likelihood that defects pass undetected. It also increases the minimum extent and severity of defects one might consider to be at ‘high risk' of being ‘filtered out'.

The results of the clinical study demonstrate the deleterious effects of over smoothing with decreases observed in defect extent and severity and increases observed in wall thickness for method B. Figure 3 illustrates this impact on short axis and horizontal long axis slices for corresponding method A and B data in a single patient. The short axis slices show the myocardium completely encroaching on the ventricular lumen and the associated increased wall thickness for method B compared to method A. The horizontal long axis slices demonstrate an apical defect being ‘smoothed out'. The clinical implications of this over smoothing are the potential for false negative findings for CAD.

Figure 4

Figure 3: Vertical and horizontal profiles through corresponding short axis slices comparing method A (top) and method B (bottom). Note the smaller ventricular lumen, broader total ventricular diameter and wider wall thicknesses for method B.



CONCLUSION

The benefits of the added functional information provided by gated SPECT of myocardial perfusion studies are universally accepted ([2,8]), however, there are a number of criteria which need to accompany gated SPECT ([2]):

- Minimal increase in cost and inconvenience of

performing gated SPECT.

- Primum non nocere, above all, do not make the patient worse ("First do no harm").

The former is an established advantage of performing gated myocardial perfusion SPECT, however, there is potential for the latter due to sources of error that may decrease diagnostic integrity. The perfusion data integrity should not be compromised by the functional data.

Not only does the generation of perfusion data via summation of the reconstructed gated data fail to provide the anticipated relief in computational demands of gated SPECT reconstruction, but it also introduces potential false negative results for CAD. This potential problem results from over smoothing and this may be particularly problematic in detecting small or non transmural defects clinically. This potential is extended to include classification inaccuracies resulting from underestimation of both the severity and/or extent of detected defects. This empirical evidence supports intuitive suspicions that the gated dataset should be ungated prior to reconstruction with gated and ungated data being reconstructed independently in parallel (or sequentially).

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